VACCINES AND HOW THEY WORK

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Infectious Diseases

Infectious diseases have been the bane of human existence throughout history. Evidence of infection has been found in mummified remains from ancient Egypt[1] and elsewhere, and in the oral and written histories of all cultures.[2] The Black Death of the Middles Ages,[3] the decimation of the native peoples of the Americas by imported disease[4] and the worldwide influenza epidemic of 1918[4] are vivid reminders that infectious diseases have profoundly shaped our world and have the potential to do so again.

Infectious diseases are caused by organisms that are able to exploit the human body so that they may grow and reproduce. In general, these organisms are tiny and can exist in our lungs, blood or other body tissues and organs. They gain access to us through the air we breathe, the food and water we ingest, or damage to our skin. Disease-causing agents (pathogens) include bacteria and viruses.[5]

Bacteria are tiny and can be seen only with the aid of a microscope. They typically are rod-shaped or round (see table below). Exposure to these pathogens occurs either by inhalation or oral uptake. However, exposure to the bacteria that cause tetanus is more commonly associated with puncture or laceration injuries or other damage to the skin, and the disease symptoms result from a toxic chemical (toxin) that the bacteria produce and release. The diseases caused by the bacteria listed in the following table can be prevented by vaccines licensed for use in the US.

Bacteria	Bacteria Shape	Disease Bacteria Causes
Corynebacterium diphtheriae	Rod	Diphtheria
Clostridium tetani	Rod	Tetanus
Bordetella pertussis	Rod	Pertussis
Haemophilus influenzae type b	Rod	Hib disease
Neisseria meningitidis	Round	Meningococcal disease
Streptococcus pneumoniae	Round	Pneumococcal disease

Viruses are smaller than most bacteria, can be seen only with an electron microscope and are much simpler in terms of their biochemical composition and biological activity. Viral diseases that can be prevented by vaccines licensed for use in the US include hepatitis A, hepatitis B, polio, influenza, measles, mumps, rubella (German measles) and varicella (chickenpox). Upon infection, viruses typically enter individual cells that make up the target tissue, e.g., the hepatitis A and hepatitis B viruses enter cells of the liver. Because viruses lurk within the cells of the body, the development of anti-virus vaccines employs strategies different from those used in the development of vaccines against bacterial pathogens. These differences are described below.

Exposure to Pathogens

Bacteria and viruses are found everywhere in our environment[6] and cannot be avoided. Most cause no health problems and some are even beneficial, such as those that live in the human intestine and aid the digestive process. Some, such as those mentioned above, clearly cause disease, while others occasionally may be responsible for disease in certain individuals. Disease results when a pathogen becomes established in a person and is associated with damage to host tissues as a consequence of its growth and reproduction, or the release of toxins.[7] This occurs in two steps: the host must first be exposed to the pathogen, and secondly, infection must occur. While scientists agree that disease develops as a result of this process, the required amount of the pathogen that the body must be exposed to in order for infection to result is much debated. Indeed the majority of infections do not result in disease.

GLOSSARY TERMS

Acquired immunity
Acute
Antibody
Antigen
Association
Asthma
Attenuated vaccines
Autoimmune disease
B cell
Bacteria
Booster
Bordetella pertussis
Cases
Causal association
Cell-mediated response
Chemokines
Chickenpox
Chronic
Clostridium tetani
Combination vaccine
Conjugate vaccine
Corynebacterium diphtheriae
Cytokines
Cytotoxic T cell
Diabetes
Diphtheria
Disease
Dysfunction
Epidemic
German measles
Haemophilus influenzae type b
Helper T cell
Hepatitis
Hepatitis A
Hepatitis B
Hexavalent vaccine
Immunization
Influenza
Innate immunity
Lymphocytes
Macrophage
Measles
Mumps
Neisseria meningitidis
Neonate
Pathogens
Pentavalent vaccine
Pertussis
Pneumococcal disease
Pneumococcal polysaccharide
Pneumonia
Polysaccharide
Polysaccharide vaccine
Protein
Rabies
Recombinant DNA technology
Risk
Rubella
Smallpox
Specific acquired immunity
Streptococcus pneumoniae
Subunit vaccines
T cell
Tetanus
Toxin
Type I diabetes
Vaccine
Vaccine schedule
Valent
Varicella
Virus
White blood cells

ACRONYMS

DNA	Deoxyribonucleic acid
Hib	*Haemophilus influenzae* type b
IOM	Institute of Medicine
MHC	Major histocompatibility complex

WEB RESOURCES

American Institute of Immunology
http://library.thinkquest.org/12429/welcome.html

Cells Alive
http://www.cellsalive.com

Dalhousie University Medical Center
http://www.medicine.dal.ca/micro/education/pimunit/home.htm

Davidson College
http://www.bio.davidson.edu/courses/immunology/bio307.html

Garland Publishing
http://blink.uk.com/immunoanimations

National Cancer Institute
http://newscenter.cancer.gov/sciencebehind/immune/immune00.htm

University of California, San Diego
http://wilson-squier.ucsd.edu/research/sb/ve/immunology

University of Leicester
http://www-micro.msb.le.ac.uk/312/BS312.html

IMMUNIZATION SCHEDULES

Childhood schedule
http://www.cdc.gov/nip/recs/child-schedule.htm#printable

Adult schedule
http://www.cdc.gov/nip/recs/adult-schedule.htm

Exposure to a single pathogenic bacterial cell is considered by some to be sufficient to result in infection and disease[8] if it is able to evade all of the body's natural defenses (described below) that protect a person from infection. If this occurs, that single cell will be able to grow and divide, ultimately giving rise to sufficient numbers of daughter cells to trigger disease. However, the development of disease following infection is more likely to occur if the host is exposed to large numbers of pathogens versus a single cell. Hence, disease is more likely to occur if the person is exposed to 10,000 pathogenic bacteria than if exposed to 1,000 or 100 bacteria.

Natural Defenses Against Infection

Human beings are protected against infectious diseases by various physical and biochemical factors.[9-11] Our first level of protection against disease is our skin and its acidic secretions, tears and the mucous membranes that line our nose, mouth and other passages connecting our internal and external environments. These factors and others, when functioning properly, keep pathogens at bay.

If an infectious agent, a pathogen, gets past the first line of defense, our bodies have a second tier of defense provided by natural or innate immune mechanisms.[12-14] In this case, our own cells and the chemicals they produce seek out, identify and eliminate the pathogen. These very general and non-specific responses are critical to the maintenance of good health.

On occasion, a pathogen can get past our bodies' primary protective mechanisms if it is present in very large numbers or if it has evaded or suppressed these processes. Stronger protection is needed, and we respond by mounting an acquired immune reaction specific to the pathogen. These responses involve a variety of types of cells found in the blood and tissues and can require a week or more to become established. Acquired immunity consists of antibody and cell-mediated responses.

An acquired immune response can result in either short-term or long-term protection against a specific pathogen and, perhaps, against some of its close relatives. In the case of long-term protection, re-exposure to the same pathogen weeks, months or years later reactivates the response mechanisms laid down during the original exposure. This reactivation leads to rapid, effective elimination of the agent, often without clinical symptoms or signs of infection. When specific immunity results from unintentional exposure to agents in the environment, we refer to the resulting protection as being passively acquired immunity. Intentional exposure to such an agent or its components through vaccination is known as actively acquired immunity.[15]

Natural Innate Immunity

Understanding how vaccines work requires some appreciation of the cells and other factors that play a role in the acquisition of immunity. The immune system is a complex network of molecules, cells and tissues that is widely dispersed throughout the body.[9-11] Each of these entities has a distinct role to play, and all interact in a coordinated and orchestrated manner to generate a timely and effective immune response to a pathogen or to a vaccine.

When a pathogen or vaccine enters the body through inhalation, ingestion, a wound or injection, the cells in the surrounding tissues release chemicals called chemokines and cytokines that attract various types of white blood cells to the area of injury, leading to the destruction of the pathogen.[16] White blood cells are found in everyone's blood and are responsible for keeping our bloodstream and tissues free of pathogens, abnormal cells and other unwanted material. Several types of white blood cells are critical to the natural immune response. One type of white blood cell is called a macrophage. It is among the first of the responding cells to arrive at the site of injury where it engulfs and destroys the pathogen.

Other types of white blood cells, called lymphocytes, also are attracted to the site. These cells, along with the macrophages release other chemokines and cytokines that direct the immune response. The local accumulation of the various types of cells contributes to the inflammation or redness that is often observed at sites of infection and injury. These cells and processes constitute the natural immune response and are often sufficient to clear or eliminate the infection.

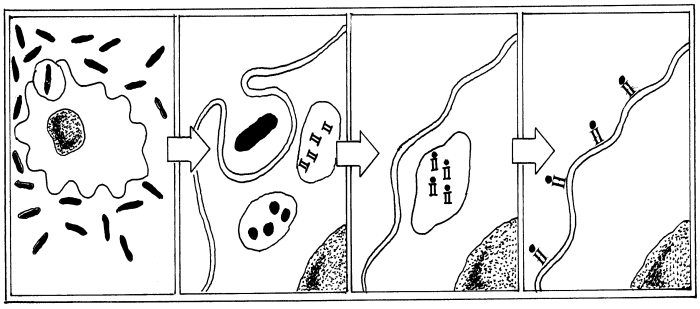
Innate immunity is neither specific nor long lasting. This response occurs each time there is a threat of infection, and is virtually identical for each pathogen that gains entry. Natural immunity is also independent of the number of times a person is exposed to any single agent, that is, even if a person is exposed to a single agent many times, their response to each exposure is the same.

Acquired Immunity – Antibody Response

Induction of a specific, protective immune response, i.e., acquired immunity, enhances the natural response by directing certain interactions among the cells participating in the immune response. Conditions for these interactions are met when the number of pathogens is large or when the pathogens are not readily eliminated by the natural mechanisms.

Macrophages play a critical role in the establishment of specific acquired immunity.[10,11] (See Figure 1 below.) As macrophages engulf an infectious organism or a certain vaccine, the organism

Figure 1



(1) (2) (3) (4)

(1) A macrophage in the presence of an infectious agent

(2) The macrophage engulfs and breaks down the infectious agent into small fragments

(3) The fragments bind to MHC Class II molecules that are produced by the macrophage

(4) Complexes of antigen fragments and MHC Class II molecules are transported to the macrophage surface

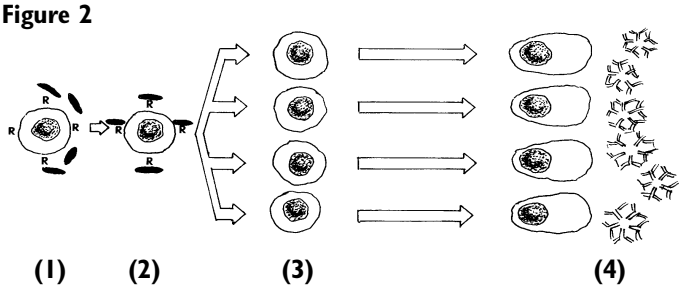
or vaccine is broken down chemically into constituent proteins and other biochemical components. The proteins are further degraded and the resulting small fragments of protein associate with certain molecules, known as major histocompatibility complex (MHC) Class II molecules, that are produced by the macrophages. These complexes, consisting of the protein fragment or antigen and the MHC Class II molecule, are arrayed on the surface of the macrophage where the antigen can be "presented" to certain lymphocytes.[17,18]

Lymphocytes, specifically B lymphocytes (or B cells) and T lymphocytes (or T cells), mediate protective immunity. (See Figure 2.) Both types of cells circulate freely in the blood, and large numbers reside in the spleen, lymph nodes and other tissues where antigen exposure is likely. B cells have structures on their surface membranes known as receptors that simultaneously recognize and adhere to proteins that make up the pathogen or vaccine. This contact is sufficient to activate the B cell causing it to divide rapidly, forming hundreds if not thousands of virtually identical cells. Many of the B cells ultimately mature into plasma cells, all of which release large amounts of antibody molecules that can specifically attack the pathogen.

There are at least two distinct populations of T cells, and these are distinguishable, in part, by the types of receptors found on their surfaces. The receptor on the helper T cell simultaneously recognizes and briefly adheres to the antigen and MHC Class II complex presented by macrophages or other antigen presenting cells;[17,18] the other T cell population is discussed below. This contact, although transient, is sufficient to activate the lymphocyte, causing it to release more or different cytokines. The cytokines stimulate cells, particularly antigen-stimulated B cells, to divide and become functionally mature. (See Figure 3.) Because a pathogen or vaccine may have hundreds or thousands of distinct antigens, many different B cells are stimulated simultaneously.

This results in the production and release of many different antibodies that recognize many of the distinct antigenic components of the pathogen. Antibody molecules encountering the pathogen attach to it, providing a handle by which macrophages, other cells or other types of molecules attach to the pathogen resulting in its destruction. In other cases, aggregations of many antibody-linked pathogens are eliminated in the urine or stool.

Figure 2



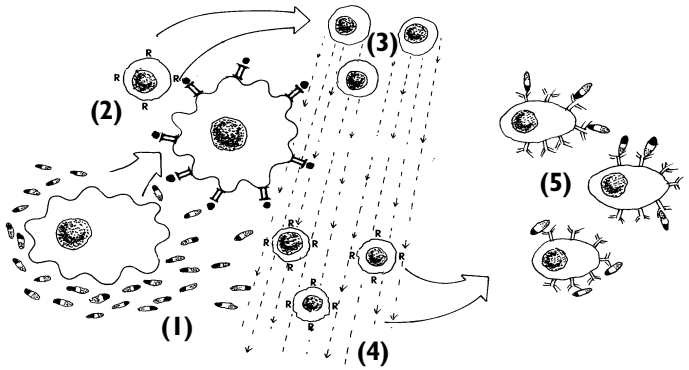
(1) B cell in the presence of an infectious agent

(2) Receptors on the B cell adhere to the infectious agent

(3) The now activated B cell divides to produce many virtually identical copies of itself

(4) The B cells mature into plasma cells that release antibodies that can adhere to the infectious agent, leading to its destruction

Figure 3



(1) Macrophages, B cells and T cells are attracted to the site of an infection

(2) The macrophage engulfs the agent and presents fragments to helper T cells

(3) Activated helper T cells release cytokines that promote B cell activity

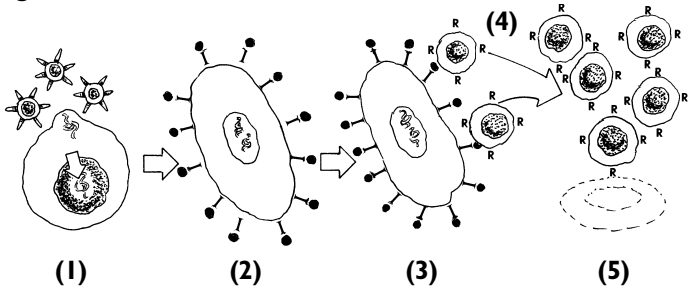
(4) Different B cells recognize different parts of the infectious agent

(5) Each B cell matures into an antibody releasing plasma cell

Acquired Immunity – Cell-Mediated Response

Antibody-mediated immunity is most effective when the pathogen occurs in the tissues and does not become established within individual cells. Other pathogens penetrate into individual cells where they can avoid interactions with antibodies and thus persist for long periods of time, causing acute or chronic disease. Viruses are particularly adept at this. When viruses infect human cells, they take over the machinery of the cell, using it to produce more copies of themselves, i.e., they replicate. (See Figure 4.) This process of replication causes fragments of virus protein to become attached to the cell's own MHC Class I molecules.[17,18] This complex attaches to the surface of the cell where the antigen is presented to T cells bearing receptors for the antigen and the Class I molecule. These T cells are called cytotoxic T cells because of their capacity to specifically destroy cells harboring the virus.

Figure 4



(1) Virus infects a cell

(2) Fragments of the virus bind to MHC Class I molecules produced by the cell

(3) The virus antigen fragments are presented to cytotoxic T cells

(4) Activated cytotoxic T cells divide to produce many virtually identical copies of themselves

(5) Activated cytotoxic T cells destroy other virus-infected cells

Again, the transient interaction between the antigen-presenting cell bearing the antigen-MHC Class I complex and the cytotoxic T cell is sufficient to activate the latter. The cell divides rapidly,

producing many, virtually identical activated cytotoxic T cells that have the capacity to destroy virus-infected cells bearing the same antigen-MHC Class I molecular complex. These T cells are thus responsible for specific cell-mediated immunity to the pathogen. This process is referred to as the cell-mediated response.

Remembering the Pathogen

The cellular interactions that produce antibodies and cytotoxic T cells occur relatively rapidly. The amount of antibodies in the blood and the number of cytotoxic T cells increase over the course of several days or weeks before they level off. As the infection is cleared or the response to immunization diminishes, some of the B cells become memory B cells and preserve on their surfaces receptors specific for the antigen that originally stimulated their parental cell.[9-11] Thus, if the individual is subsequently re-exposed to the same agent, the B memory cell is poised to respond by quickly dividing and releasing antibodies. Similarly, certain pathogen-specific cytotoxic T cells also persist as memory T cells that are available to respond more quickly and effectively should the individual be exposed again to the same agent.[9-11] Vaccination establishes a pool of memory cells that can produce pathogen-specific responses fast enough to largely prevent development of the disease and to minimize its impact on the individual.

Development of the Immune System

At birth, many of our biological systems, e.g., lungs, liver, heart and kidneys, are fully formed and fully functional. The immune system, however, is not. The various cells and tissues that comprise the system are in place, and natural immune responses are possible, but the immune system does not become fully functional until it has been exposed to antigens.[9-11]

Immunologists have long recognized that the immune system is capable of recognizing and responding to an enormous number of distinct antigens.[19] This diversity in antigen recognition capacity applies to both B cell- and T cell-mediated immunity,[11,12] and is perhaps best summarized in the context of the B cell response.

The receptors found on the surface of unstimulated B cells are composed mostly of protein. These receptors are assembled from various polypeptides (chains of amino acids that are the building blocks of proteins) during B cell development. The polypeptide components include light and heavy chains (referring to the number of amino acids in each), variable segments, joining segments and diversity segments.[11,12] As the B cell develops, each component is produced within the cell, and each is the product of a separate gene.

There are between four and 1,000 genes that can be used to direct the production of each polypeptide. Although only one of each type of polypeptide is needed to form a receptor molecule on the surface of a single cell, receptors on different B cells are produced from various combinations produced from the many available polypeptide genes. Based on the total number of genes available to produce these molecules and additional diversity enhancing processes associated with their assembly, the immune system is estimated to be able to respond to more than 10 million different antigens.[11,12]

This is, of course, the theoretical upper limit to the number of antigens recognized by the immune system. The actual number is constrained by the number of B cells present, the number of new B cells being added daily (mature B cells survive for only a few days) and various other factors.[20] But even when all of these constraints have been factored in, the ability of the immune system to recognize and respond to antigens is immense. In fact, it has been estimated that even if all of the currently recommended vaccines were given to a child at one time, they would engage less than 1% of the immune system's total antigen response capacity.[20]

Antigen exposure during postnatal development is increasingly thought to be an important prerequisite for normal immune system development. Because exposure to both benign and pathogenic microbes has been a long standing feature of human neonatal experience, such exposures may be necessary in instructing the immune system to ignore or tolerate benign organisms (such as those inhabiting the intestinal tract) while priming the neonate to be able to initiate a functionally robust immune response to potentially dangerous pathogens.[21,22]

Maintaining Immunity

Some vaccines need to be administered periodically throughout the lifespan, e.g., tetanus, or even annually, e.g., influenza. Vaccines against tetanus trigger antibody responses to a specific toxic protein made by *Clostridium tetani*, the tetanus-causing organism. Over time, the production of specific antibodies wanes to the point that there is no longer sufficient antibody or memory B cells present to protect against the toxin produced as a result of a natural infection. The waning of the response is gradual and hence, re-immunization with the tetanus vaccine is recommended at ten-year intervals after the final childhood immunization (at approximately five years of age).

Vaccines against influenza (the flu) offer a further example of the complexities of protective immunization. The influenza virus changes on a continuing basis, making it difficult to identify a stable antigen to be used in a vaccine to elicit long-lasting protective immunity. The virus also is promiscuous; it can infect a variety of non-human animals such as ducks, chickens and swine. As the virus moves from host to host, it can undergo further changes. Thus, the antigen associated with the flu-causing virus differs from year to year, necessitating the formulation and administration of a different vaccine each year.

Vaccines

Vaccination is intended to elicit a specific immune response that will protect the immunized individual from the pathogen should he or she be exposed to that agent at a later date. Such intentional exposures use inactivated or other forms of the agent that stimulate the protective response without triggering the disease.[15] The ability of a vaccine to do this is sometimes enhanced when it is combined with an adjuvant, a substance that attracts additional inflammatory cells to the vaccination site and stimulates them to release more and different cytokines. These chemical signals further stimulate and activate macrophages and lymphocytes to acquire additional protective functions.

Because of the unique properties of viruses and other intracellular pathogens, vaccines against such infectious agents ideally should elicit vigorous antibody- and cell-mediated responses. Effective vaccines stimulate the production of antibodies that

destroy the pathogen prior to its entry into cells, and elicit cytotoxic T cells that can destroy cells in which the pathogen resides. Together these responses protect against disease.

Types of Vaccines

Each vaccine is unique in terms of its composition and formulation. These differences reflect not only the different infectious agents from which the vaccines are derived, but also how the vaccines are used and the mechanisms through which their effects are mediated. The following describes various vaccine formulations in current use and gives examples of each. Each vaccine is further described and characterized in the section *Vaccines*.

Live attenuated vaccines consist of a weakened form of the infectious agent itself. The attenuated form can reproduce, thus assuring that the vaccinated person will be exposed to the agent long enough to develop a specific protective immune response. However, because the disease-causing agent is weakened, it is unable to elicit the disease in healthy people. The measles, mumps, rubella and some polio vaccines are examples of live attenuated vaccines.[23]

Inactivated vaccines may consist of intact bacteria or viruses (often referred to as whole cell vaccines) or extracts of those agents sometimes referred to as acellular, subunit or fractional vaccines. The components of these vaccines are not able to reproduce, do not cause disease and are typically given in multiple doses to elicit immune protection. Inactivated vaccines include some of those for influenza (flu), rabies, hepatitis A and B, pertussis and tetanus.[23]

Acellular and subunit vaccines are typically composed of protein extracted from the infectious agent. For example, tetanus disease is due to a toxic chemical produced by the tetanus pathogen. A weaker form of this chemical, referred to as tetanus toxoid, is the principle component of the tetanus vaccine. Other subunit vaccines include those for hepatitis B and diphtheria.[23,24] The hepatitis B vaccine is the first to be produced using recombinant DNA technology, an approach that holds great promise for speeding the development of safe and effective vaccines.

Some subunit vaccines consist of polysaccharides (long chains of sugar molecules) isolated from a specific infectious agent. Pure polysaccharide vaccines, such as some of the older vaccines against pneumococcal and meningococcal diseases and against *Haemophilus influenzae* type b, often have limited ability to elicit effective protective immunity.[23]

The response to polysaccharide-based vaccines is enhanced when the polysaccharide molecules are conjugated (bound chemically) to a carrier protein. Such conjugated vaccines elicit strong protective immunity that can be further enhanced by additional (booster) immunizations. Conjugate vaccines against pneumococcal disease in children and *Haemophilus influenzae* type b are in common use.[23]

Both pure polysaccharide and conjugate polysaccharide vaccines consist of multiple antigenic components from the target pathogen. The number of components is often used to describe the vaccine. For example, a pure polysaccharide vaccine against pneumococcal disease that contains 23 different antigenic components is referred to as a 23-valent vaccine.[25]

Vaccination of Children

Based on current immunization recommendations,[26] children in the US typically receive 11 vaccines that are administered through as many as 20 separate inoculations by the age of two years. A national telephone survey in 1999 of expectant parents and parents of children six years of age and younger revealed that 23% of parents questioned the number of immunizations recommended for children and 25% worried that the vaccines might weaken the immune system.[27]

Concerns about the number of immunizations recommended for children and the development of the immune system focus on three issues. The first is the number of inoculations given. The number of recommended inoculations reflects the number of diseases that now can be prevented by vaccination.[20] In 1900, the one vaccine that was given to children prevented one disease, smallpox. By 1960, eight immunizations by age two prevented five diseases. Currently, children can be vaccinated against 11 vaccine-preventable diseases. In most cases, the recommended vaccines require an initial priming immunization and one or more booster immunizations to achieve full, long-lasting protective immunity.

A second aspect of parental concern is the ability of a child's immune system to recognize and respond to all of the antigens that are introduced when a child is vaccinated according to the current vaccine schedule. Vaccines, like the disease agents they mimic, are composed of many different proteins or other molecules that may be recognized by the immune system. Indeed, the smallpox vaccine given to children in 1900 was estimated to consist of about 200 different antigens and the 1960 formulation of the pertussis vaccine used whole cells of *Bordetella pertussis*, which are estimated to consist of approximately 3,000 different proteins.[20] Through advances in how vaccines are developed, the 11 vaccines in current use consist of 123-126 antigens,[20] a small number relative to immune system's capacity to recognize and respond to antigens as described above.

The third aspect of parental concern about childhood immunization is whether exposure to these 123-126 antigens compromises the development of the child's immune system. The Institute of Medicine's (IOM's) Immunization Safety Review Committee recently examined the scientific evidence surrounding this issue.[22] The committee asked whether multiple immunizations were associated with various types of immune dysfunction that might result from impaired immune system development.

The committee found no epidemiological evidence supporting a causal association between multiple immunizations and an increase in the incidence of infections by other pathogens or an increase in the likelihood of developing type 1 diabetes, an autoimmune disease associated with immune dysfunction. There was insufficient information available to assess whether multiple immunizations might increase the risk of allergic disease. Given what is currently known about biological mechanisms associated with the development of autoimmune and allergic diseases, the committee concluded that multiple immunizations could be only theoretically or weakly linked to such immunological dysfunctions. There was stronger evidence of a possible mechanistic link between multiple immunization and susceptibility to other

pathogens, although this was not borne out by the epidemiological data.[22] The findings of this committee are described in greater detail in the *Vaccine Safety Issues* section.

Vaccination of Adolescents and Adults

The current adult immunization schedule[28] calls for people over 21 years of age to receive regular (every 10 years) booster immunizations against diphtheria and tetanus, annual influenza immunizations for persons 50 years of age and older, and pneumococcal immunization at age 65 years. Influenza and pneumococcal vaccines are also recommended for younger adults and adolescents with chronic illnesses such as heart, lung or liver disease, diabetes and asthma. In addition, adults not previously immunized against measles, mumps, rubella or varicella, or who have no documented history of having these diseases, are encouraged to obtain these immunizations. Adults at risk for hepatitis A or hepatitis B exposure also are encouraged to receive the appropriate immunizations.

The number and frequency of vaccinations recommended in the adult immunization schedule is much reduced relative to those given to children. Except for immunizations that might be required by certain employers, e.g., healthcare providers, or in conjunction with military service, none of the adult recommendations is backed by enforceable mandates.

Trends in Vaccine Development

Vaccine research and development and the tools of modern biotechnology have resulted in the licensing and use of vaccines that are safe and effective. Researchers continue to seek new approaches to reducing the number of inoculations given and, in some cases, eliminating the use of needles for administering vaccines.

Combination vaccines such as MMR, DTaP, pneumococcal polysaccharide and others have been used in the US for many years,[29] and a new combination vaccine against both hepatitis A and hepatitis B was licensed in 2001.[30] Other combination vaccines are under development. For example, a vaccine that offers protection against diphtheria, pertussis, tetanus, hepatitis B and polio has undergone extensive clinical testing that has shown it to be safe and effective.[31] If licensed and used in the US, this pentavalent vaccine could reduce the number of primary series vaccinations given to children from nine to three. Both pentavalent and hexavalent vaccines are licensed for use in several European countries.[32] Although the introduction of additional combination vaccines could further reduce the number of inoculations given,[33] their development, licensing and manufacturing is complex.[33-35]

Other new and emerging developments related to vaccine administration include the potential use of inhaled or intranasal vaccines. Because many diseases result from inhaling pathogens, vaccines delivered to the lungs could produce a strong immune response capability in the lungs, thus providing highly effective protection against disease. Intranasal vaccines against influenza,[36,37] hepatitis B,[38] meningococcal disease[39] and others[40,41] are under active investigation. Additional needle-free approaches to vaccination include the use of skin patches[42] similar in design to those used to prevent motion sickness, using compressed air to painlessly propel microscopic vaccine-coated particles into the skin,[43] and incorporating vaccines into edible plants.[44] These and other approaches are still under development, but offer hope that someday syringes and needles will be relegated to museums.

Vaccines and Disease Prevention

Vaccines are designed to protect us from the consequences of infectious disease. This is accomplished by exposing the individual to inactivated or other forms of the pathogen, giving rise to antibodies, B cells and T cells that protect the individual from the debilitating and often life-threatening consequences of infectious disease. Vaccines are unique among modern medications in that they offer effective protection against the onset and progression of specific infectious diseases. Most other medications are therapeutic, i.e., they are used to treat the disease and/or its symptoms; few are preventive. Vaccination is also unique in harnessing the cells, tissues and molecules of an individual's immune system to mediate this protection through a variety of natural mechanisms and processes that are fundamental to human biology. The development and use of safe, effective vaccines has and will continue to contribute significantly to our increasing life expectancy and to the quality and richness of our lives.

Vaccines and the Quality of Life

In addition to their ability to prevent disease among both immunized and non-immune members of the community, vaccines can make substantial contributions to the quality of life of families and communities. Disease prevention results in substantial cost savings whether measured by personal, family, insurer or community expenditures. Vaccines reduce the need for visits to physicians' offices, hospital admissions, medication use and other medical care. In addition, effective immunization programs that protect individuals and limit the transmission of disease within a community, contribute to better school attendance by healthier students, the maintenance of a healthy and reliable workforce, and reduce the amount of time devoted to visits to doctors offices, clinics or caring for ill children, family members or others. Communities embracing the use of vaccines to protect the health of its members are also likely to endorse other preventative practices and policies, e.g., car seat usage, programs to reduce drug, alcohol and tobacco use and others, that further enhance community health and the quality of life.[45]

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SCIENTIFIC STUDIES OF VACCINES

SCIENTIFIC STUDIES OF VACCINES

Scientific studies are conducted throughout the many stages of vaccine research, development, licensure and general use. Results of studies on the prevalence and burden on society of a particular disease help manufacturers and advisory committees decide whether developing a particular vaccine would be useful to the public. Market and social research conducted prior to the development of a vaccine helps manufacturers determine a vaccine's potential profitability. Laboratory studies help researchers and manufacturers to develop quality, safe vaccines that provide protection against infectious disease. Scientific research helps federal agencies evaluate whether a vaccine is safe and effective enough to be licensed for use by the general public. Surveillance studies conducted following a vaccine's licensure and its widespread use provide ongoing assessment for manufacturers, government agencies, state and local health departments, independent agencies and the public of the vaccine's safety and effectiveness. Such studies also provide evidence to the public of the safety, value and importance of vaccines for themselves, their families and their communities.

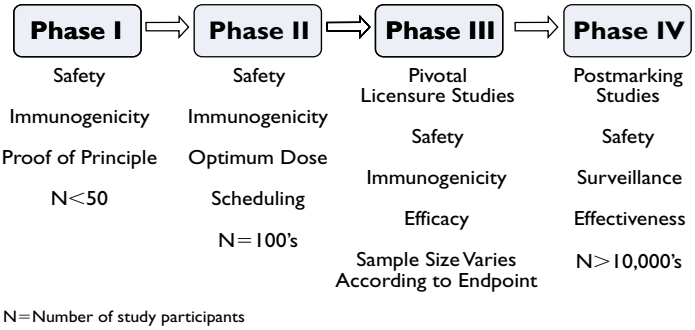
Evaluation of Need

The first step in vaccine development is to determine whether a vaccine to protect against a particular disease is needed. Such identification requires an understanding of the disease that the potential vaccine would protect against, its burden on both the general population and on particular risk groups, disease treatments currently available and the costs associated with treating the disease. Surveys and reviews of medical records are often used to find this information. These studies provide justification to the potential vaccine sponsor (an individual physician, university, hospital, government agency or commercial firm/manufacturer) that the development of a particular vaccine would be necessary or desirable by either the general public or a specific risk group. From a commercial perspective, such studies can indicate whether the vaccine would be profitable or in the best interest of the sponsor to produce.

Vaccine Development

Once the development of a vaccine has been deemed necessary by the vaccine sponsor, laboratory tests must be conducted in order to identify the antigen(s) that can be used in the vaccine to elicit an immune response against a particular disease. Animal studies are often critical at this stage of vaccine development and may also be used to provide evidence that the antigen used in the vaccine is safe and is able to trigger a strong immune response. If these studies produce a viable vaccine that provides a certain level of protection in animal models, clinical studies can be initiated.

The Stages of Vaccine Clinical Trials



N=Number of study participants

The above diagram summarizes the types of studies conducted in humans that occur during the development of a safe and effective vaccine. Phase I clinical vaccine studies are conducted to evaluate safety and immunogenicity. The first studies are conducted in a small number of healthy study participants who are at low risk for infection to determine whether the vaccine can be used safely in humans. Additional Phase I studies may be conducted to provide vaccine safety data for other populations,

GLOSSARY TERMS

Adverse events
Antigen
Association
Bias
Blinded
Case-control studies
Cases
Case series
Causal association
Clinical trial
Cohort studies
Confounder
Controls
Cross-sectional studies
Disease
Dose-response relationship
Ecologic studies
Efficacy
Immunogenicity
Incidence
Mumps
Odds ratio
Prevalence
Prospective cohort studies
Relative risk
Retrospective cohort studies
Risk
Rubella
Temporal relationship
Threshold
Vaccine
Vaccine sponsor

WEB RESOURCES

Centers for Disease Control and Prevention
http://www.cdc.gov/nip/vaccine/develop-approval.htm

e.g. minority groups, populations at high-risk for disease, immunosuppressed persons, etc. If the vaccine is found to be safe and immunogenic in these study participants, Phase II clinical trials are initiated. The objective of Phase II vaccine trials is to determine the optimum vaccine dose and schedule to obtain maximum protection from the disease. These studies are performed in the proposed target group, e.g., adults, children or others at risk of exposure to the pathogen. The results of Phase I and II studies determine whether the vaccine sponsor will proceed to a large Phase III trial to determine the vaccine's efficacy.

If the decision is made to proceed to a Phase III efficacy trial, the size and duration of the trial will be determined by many factors. Trial size must take into account disease prevalence in the population being studied and the study must continue long enough to be able to at least partially assess how long the vaccine will protect a person from developing the disease. A single, definitive Phase III trial may provide sufficient efficacy data for licensing a vaccine, but other trials may be necessary.

Types of Studies Utilized

In the effort to evaluate the value and safety of vaccines at all stages of vaccine research, development, licensure and general use, researchers can utilize several types of study methods. Different studies are utilized depending on the type of information desired or the research question being raised. An understanding of the strengths and weaknesses of each study method assists in the assessment of a study's conclusions. Study biases constitute a major flaw in study methods and should be avoided. A bias is any systematic error in the design, methods or conclusions of a study that results in a mistaken estimation of the vaccine's effect on the risk of a particular disease.[1] These errors make study interpretations difficult as strong preconceptions by researchers may unintentionally affect data analysis and interpretation.[2]

A. Ecologic studies: These studies look at group characteristics and often are the first approach used by researchers in determining whether or not an association exists.[2]

Strengths: Ecologic studies allow researchers to use types of data that are easy to obtain such as registries, birth certificates, average values for disease rates, vaccine uptake, etc. These studies can suggest avenues of research that may cast more light on whether an exposure led to adverse events or whether an adverse event led to a symptom.[2]

Weaknesses: Because these studies use group data, they are unable to account for variability among individuals within a group. Thus, characteristics could be attributed to members of a group that do not in fact possess these characteristics as individuals. Therefore, ecologic studies alone cannot demonstrate that a causal association exists.[2]

B. Studies of individual characteristics: e.g., case-control, cohort and cross-sectional studies.

(1) Case-control studies: In one form of a case-control study, researchers identify a group of persons with the adverse event (cases) and a group of persons without the adverse event (controls) and then determine the proportion of each group that was exposed to the vaccine. In another form of these studies, researchers compare the prevalence of adverse events in vaccinated and unvaccinated cases.[2]

Strengths: Case-control studies are relatively inexpensive and require fewer study participants than cohort studies. This strength is especially important if the adverse event under study is rare, making the identification and recruitment of study participants difficult.

Weaknesses: Because case-control studies require data about whether a person was vaccinated or not, participants may have forgotten this information. Selection of a control group is extremely difficult and can also introduce numerous biases.[2]

(2) Case series: Researchers identify cases exposed to the vaccine that has been identified as a proposed risk factor for a certain adverse event. These cases are followed through time and evaluated for the development and severity of any adverse event that may occur. Case series studies do not compare adverse event development and severity of the adverse event in unvaccinated groups versus vaccinated groups.[2]

Strengths: This study method allows researchers to do extensive studies on a small group of people known to have the adverse event under study and may identify temporal patterns of the appearance of the adverse event after immunization. Case series are useful when the vaccine being studied is administered to nearly all persons in a population and, therefore, few unvaccinated persons are available for study.[3]

Weaknesses: Without knowing whether the adverse event would also develop in the unvaccinated population, researchers cannot conclude definitively that the vaccine caused the adverse event. Controls similar to cases in all factors other than having been vaccinated with a particular vaccine are necessary in order to demonstrate that the vaccine and not some other factor is responsible for causing the adverse event.[3]

(3) Cohort studies: Researchers select a group of individuals exposed to the vaccine and a group of individuals who were not exposed to the vaccine and follow both groups to compare the number of new cases of adverse event (or rate of death from the adverse event) in the two groups over time. This information is usually obtained from past medical records and death certificates.[2]

Strengths: These studies are an excellent means of identifying causal relationships as the study design eliminates many of the biases that can be introduced in the selection of cases and controls. Cohort studies should be used when good evidence exists that vaccine use is associated with an adverse event.[2]

Weaknesses: Cohort studies can be very lengthy and expensive. Researchers who determine whether the adverse event developed may be biased due to knowledge of participant exposure or other presenting characteristics if they are not "blinded" or kept unaware of this information. The quality and extent of information obtained in the study may differ between

vaccinated and unvaccinated persons or persons classified either as having or not having the adverse event or by the loss of participants to follow-up over time.

(a) Prospective cohort studies: Researchers identify the groups of individuals to be used in the study at the beginning of the study and follow the individuals through time until the adverse event does or does not develop. Exposure to the vaccine is determined as it occurs during the study and the groups are followed for several years to measure the adverse event incidence. These studies assess the vaccination status of study participants and determine, with strong validity, if the adverse event develops after exposure to the vaccine being evaluated.[2] The vaccine can only be implicated as causing the adverse event if administration of vaccine occurs prior to the development of the adverse event.

Strengths: Prospective cohort studies introduce fewer biases by researchers as the study progresses.

Weaknesses: These studies can be extremely lengthy and expensive.

(b) Retrospective cohort studies: Researchers use past historical data to define a study period and obtain study results more quickly. Exposure to the vaccine is determined using past records and/or data taken at the beginning of the study on whether the study individuals have developed the adverse event.[2]

Strengths: Retrospective cohort studies require less time, resources and funding than prospective studies.

Weaknesses: Due to their reliance on past records that may not be complete, accurate or fully applicable (and therefore may require interpretation); retrospective studies are often less useful than prospective studies and are more prone to investigator bias.[2]

(4) Cross-sectional studies: Researchers determine both vaccine exposure and adverse event outcome simultaneously. Disease prevalence rather than incidence is used. Therefore, cross-sectional studies do not include persons who died after the disease developed but before the study was initiated.[2]

Strengths: Cross-sectional studies require less time and often are less expensive than cohort or case-control studies.

Weaknesses: These studies cannot determine whether vaccine use in study participants preceded the development of the adverse event. Instead cross-sectional studies can only suggest a possible risk factor for an adverse event.[2]

Post-Licensure Evaluation

The pre-licensure Phase I, II and III studies described above provide close, detailed follow-up of study participants that allows for easy causality assessment. However, these studies cannot adequately detect rare or delayed adverse events nor adequately evaluate how various sub-populations of people might respond to certain vaccines. Historically, populations in pre-licensure studies have been fairly homogeneous, often including primarily young, healthy Caucasian males. More recent prelicensure studies include a more heterogeneous group of people more closely reflecting the diversity of the US population. But post-licensure studies of large populations over longer periods of time are necessary to provide ongoing assessment of vaccine safety and effectiveness.[4]

If the safety of a vaccine is questioned by national surveillance mechanisms (see page 21), by research studies or by public concern, a two-step evaluation process of the vaccine in question takes place. First, studies are conducted to determine whether there is an association between the vaccine and either an adverse event or risk of a particular disease. If an association is demonstrated, the second step is to conduct studies to ascertain whether the observed association is likely to be a causal one.

Analysis of a highly publicized 1981 study on coffee consumption and pancreatic cancer demonstrates the distinction between association and causation. Investigators noted that persons who drank more coffee had higher rates of pancreatic cancer, especially women. This finding initially led researchers to believe that drinking coffee caused pancreatic cancer.[5] Critiques of this study noted that most people who smoke also drink coffee and hence, the increased risk of pancreatic cancer was more likely to be caused by smoking rather than coffee drinking.[2] Several years later, another group of investigators attempted to replicate the original study findings while accounting for the smoking status of study participants. However, the association was no longer apparent in this second study.[6] This example highlights the importance of carefully assessing safety studies to determine whether an identified association is or is not causal.

Causal Assessment

During the debate over the possible link between smoking and lung cancer, the US Surgeon General appointed an expert committee to review the evidence. This committee developed a set of guidelines that have since been revised and utilized to assess whether or not an association is causal.[7] The following is the list of these guidelines as they might be applied to evaluating associations between vaccines and their possible adverse events:

1. **Temporal relationship:** If a vaccine is believed to be the cause of a particular adverse event, exposure to the vaccine must occur before the adverse event develops.

2. **Strength of the association:** This criterion is measured by the relative risk or odds ratio. Relative risk is measured by dividing the incidence of the particular event in vaccinated individuals by the event incidence in unvaccinated individuals. If the relative risk is equal to one, the risk of the event occurring is the same in both the vaccinated and unvaccinated groups, indicating no increased risk of the event in either group or for any association of the event with the vaccine. If the relative risk is greater than one, the risk of the event occurring is higher in the vaccinated group as compared to the unvaccinated group, thus providing evidence of a positive association between vaccination and the

event that may be causal. The stronger the association, i.e., the greater the relative risk value, between the vaccine and the adverse event, the more likely it is that the relation is causal. A relative risk ratio less than one indicates that the risk of the event occurring is higher in the unvaccinated group as compared to the vaccinated group, thereby suggesting a negative association that may indicate that the vaccine actually protects the individual from the event. In some studies, relative risks cannot be calculated because data on actual event incidence does not exist or the risk of the event is low. Odds ratios are often used in such cases to estimate the relative risk. Odds ratios use prevalence estimates to calculate the ratio between vaccinated and unvaccinated individuals of the chance that an event will occur rather than a ratio of actual event incidence.

3. **Dose-response relationship:** As the amount or number of doses of vaccine increases, the risk of the adverse event should also increase. The absence of a dose-response relationship does not necessarily rule out a causal relationship. In some cases, no adverse events will develop until a certain level of vaccine exposure (a threshold) is reached; above this level, the adverse event may develop.

4. **Replication of findings:** If the relationship is causal, the relationship between a vaccine and an adverse event should be seen consistently in different studies and in different populations.

5. **Biologic plausibility:** This criterion refers to coherence with current biologic knowledge. Although epidemiologic observations have sometimes preceded biologic knowledge, a biological explanation of the mechanisms by which the vaccine causes the adverse event lends enormous weight to the conclusion that the association is causal.

6. **Consideration of alternative explanations:** Are there other agents or factors that have been suggested or identified as risk factors for the adverse event? Reports suggesting a causal association should thoroughly account for any factors other than the one in question that may alter study results/analyses (confounders) in their analyses.

7. **Cessation of exposure:** The risk of the adverse event occurring should decline if exposure to the vaccine in question is reduced or eliminated. In the case of vaccines, the disease process may be irreversible following an initial exposure to the vaccine.

8. **Specificity of the association:** If an adverse event only occurs after being vaccinated with a particular vaccine, a specific association exists. When specificity of an association is found, it provides additional support for a causal relationship. However, absence of specificity in no way negates a causal relationship.

9. **Consistency with other knowledge:** Strong evidence that a vaccine does cause an adverse event includes findings that show the association to be consistent across different geographic populations, ages, sex and ethnicities. However, causal associations can also exist that are very specific to a particular group of people.[2,7]

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FEDERAL REGULATION, SURVEILLANCE AND EVALUATION OF VACCINES

FEDERAL REGULATION, SURVEILLANCE AND EVALUATION OF VACCINES

Vaccine Licensure

The regulation of vaccines begins with the extremely lengthy and rigorous process of vaccine licensure. The Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA) is the United States agency that is responsible for regulating and licensing vaccines.[1] CBER reviews applications for licensure of vaccines, biologicals and blood products as well as evaluates the establishments that produce these products, enforces compliance with FDA standards and conducts post-marketing product surveillance.

However, vaccine regulation requires the coordination and assistance of many government agencies. CBER works with many organizations to fulfill these responsibilities. The chart below describes the roles that the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH) and the National Vaccine Program Office (NVPO) play in this process.[3]

Organization	Role
Centers for Disease Control and Prevention (CDC)	Responsible for disease surveillance and for support of immunization programs
National Institutes of Health (NIH)	Conducts and funds biomedical research
National Vaccine Program Office (NVPO)	Coordinates the vaccine efforts of the US Public Health Service and the Interagency Vaccine Group (IAVG). IAVG consists of the following organizations:
	• Agency for International Development (USAID)
	• Centers for Disease Control and Prevention (CDC)
	• Department of Defense (DoD)
	• Food and Drug Administration (FDA)
	• Centers for Medicare and Medicaid Services (CMS)
	• National Institutes of Health (NIH)
	• Office of the General Counsel (OGC)

The diagram on page 18 illustrates the process a vaccine sponsor must go through to license a vaccine for public use. Licensure is a long and expensive process. Fulfilling the licensure requirements of CBER takes between 5 and 10 years and costs between $300 and $500 million.[2] Even if the vaccine is licensed, federal oversight continues for as long as the vaccine remains licensed in the United States.

Investigational New Drug (IND) Application

The process of vaccine licensure begins when a vaccine sponsor files an Investigational New Drug (IND) application. This application sets into motion a systematic and in-depth evaluation of the safety and efficacy of the vaccine that may or may not result in licensure of the vaccine for use in the US. The IND application must meet FDA's strict review criteria before clinical studies can begin on the candidate vaccine. The IND application must explain the scientific rationale for the vaccine, describe the vaccine and the manufacturing process required to produce it, describe all pre-clinical study data, and propose a plan for a Phase I clinical trial. Pre-clinical study data must demonstrate that the vaccine has passed a series of tests for purity (laboratory tests) and safety (studies in animals). Information contained within the

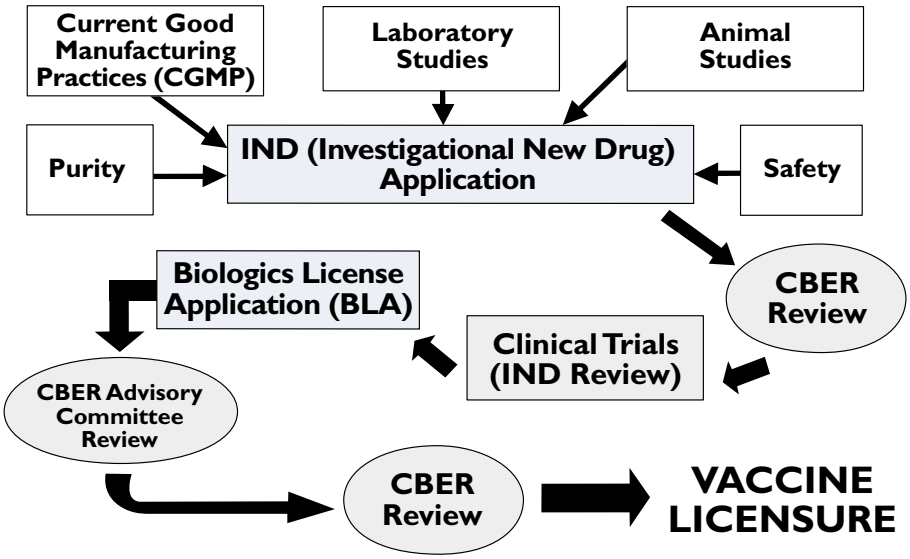
GLOSSARY TERMS

Adverse events
Advisory Committee on Immunization Practices (ACIP)
Allergy
Anthrax
Association
Attributable risk
Autism
Bias
Cases
Clinical trial
Compulsory immunization laws
Contraindications
Controls
Coverage
Current Good Manufacturing Practices
Diabetes
Diphtheria
Disease
Efficacy
Epidemic
Epidemiologic studies
Excise taxes
Guillain-Barré syndrome
Haemophilus influenzae type b
Hepatitis
Hepatitis A
Hepatitis B
Immunization
Inflammatory bowel disease
Influenza
Intussusception
Measles
Meningococcal disease
Mumps
Pertussis
Pneumococcal disease
Pneumococcal polysaccharide
Poliomyelitis
Polysaccharide
Polysaccharide vaccine
Pre-clinical study
Registry
Risk
Rotavirus vaccine
Rubella
Safety assessment
Seizure
Smallpox
Tetanus
Thimerosal
Vaccination registry
Vaccine
Vaccine Identification Standards Initiative
Vaccine Information Statement
Vaccine Injury Compensation Program
Vaccine Safety Datalink Project
Vaccine schedule
Vaccine sponsor
Varicella
Virus

ACRONYMS

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research (FDA)
CDC	Centers for Disease Control and Prevention
CGMP	Current Good Manufacturing Practices
CISA	Clinical Immunization Safety Assessment
CMS	Centers for Medicare and Medicaid Services
COID	Committee on Infectious Diseases (AAP)
DHHS	United States Department of Health and Human Services
DoD	Department of Defense
DTaP	Diphtheria, tetanus, acellular pertussis vaccine
FDA	Food and Drug Administration
Hib	*Haemophilus influenzae* type b
HMO	Health maintenance organization
HRSA	Health Resources and Services Administration
IAVG	Interagency Vaccine Group
IND	Investigational New Drug
IOM	Institute of Medicine
IPV	Inactivated poliovirus
IRB	Institutional Review Board
MMR	Measles, mumps, rubella
MSAEFI	Monitoring System for Adverse Events Following Immunization
NIH	National Institutes of Health

(continued)



IND application must, according to the Code of Federal Regulations, demonstrate compliance with the minimum standards for Current Good Manufacturing Practices (CGMP), which are federally mandated regulations that define requirements for the manufacturing process, quality control, documentation, testing and facilities.[4,5] The FDA may require that additional studies be conducted or that alterations be made throughout the manufacturing process.[3]

CBER has 30 days to complete the initial review after the complete IND application has been received. At the end of this time, a decision is made either to approve the application (and allow the vaccine to enter clinical trials) or to request additional information from the sponsor. However, even if approved, CBER review continues until the vaccine is licensed. Routine inspections and reviews are ongoing and a vaccine can be placed on "clinical hold" at any time during this process if, for example, CBER requests that further studies be done or requires that alterations be made to the manufacturing process.[5]

Institutional Review Board (IRB)

In addition to receiving IND application approval, a local, outside body of experts known as an Institutional Review Board (IRB) must also approve the study before the candidate vaccine can enter clinical trials. An IRB is a committee established by the agency, institution or corporation conducting the clinical trial to review all aspects of the study. Such committees typically include scientists, physicians and other professionals as well as individuals from the community. One crucial role of the IRB is to oversee the development and use of informed consent forms that must be signed by vaccine study participants. The FDA requires that all clinical studies provide study participants with information on the types of tests/procedures they will be subject to under the study, why these tests are being conducted and what known risks, if any, are involved in taking part in the research study. After this information is provided, individuals must sign consent forms to provide documentation that they understand and agree to the terms of participation in the study and have been made aware of the risks involved.[3]

Clinical Studies

After both CBER and the study's IRB have given the vaccine sponsor permission to move forward with clinical studies, the vaccine can enter a Phase I clinical study. Clinical studies required for licensure must move through Phase I, II and III studies as described on pages 13–14. IRB approval must be given prior not only to the initiation of Phase I studies but also to Phase II, Phase III and Phase IV studies. These trials are constantly monitored and reviewed by CBER and can be halted,

NVAC	National Vaccine Advisory Committee
OGC	Office of the General Counsel
PHS	Public Health Service
USAID	United States Agency for International Development
VAERS	Vaccine Adverse Events Reporting System
VICP	Vaccine Injury Compensation Program
VIS	Vaccine information statement
VISI	Vaccine Identification Standards Initiative
VNPO	National Vaccine Program Office
VRBPAC	Vaccines and Related Biological Products Advisory Committee (CBER)
VSD	Vaccine Safety Datalink Project

WEB RESOURCES

FEDERAL VACCINE REGULATION:

Center for Biologics Evaluation and Research (CBER)
http://www.fda.gov/cber/index.html

Centers for Disease Control and Prevention
http://www.cdc.gov/nip/vaccine/develop-approval.htm

Executive Summary of the Task Force on Safer Childhood Vaccines
http://www.niaid.nih.gov/publications/vaccine/safervacc.htm

Food and Drug Administration (FDA)
http://www.fda.gov

National Vaccine Program Office (NVPO)
http://www.cdc.gov/od/nvpo

Vaccine Information Statements (VIS)
http://www.cdc.gov/nip/publications/VIS/default.htm

Vaccines and Related Biological Products Advisory Committee
http://www.fda.gov/cber/advisory/vrbp/vrbpmain.htm

NATIONAL VACCINE PROGRAM INTERAGENCY GROUP:

Agency for International Development (USAID)
http://www.usaid.gov

Centers for Disease Control and Prevention (CDC)
http://www.cdc.gov

National Immunization Program
http://www.cdc.gov/nip

National Center for Infectious Diseases
http://www.cdc.gov/ncidod/index.htm

Centers for Medicare and Medicaid Services (CMS)
http://cms.hhs.gov

Department of Defense (DOD)
http://www.defenselink.mil

Health Resources and Services Administration (HRSA)
http://www.hrsa.gov

National Vaccine Injury Compensation Program (NVICP)
http://bhpr.hrsa.gov/vicp

National Institutes of Health (NIH)
http://www.nih.gov

National Institute for Allergy and Infectious Diseases (NIAID)
http://www.niaid.nih.gov/default.htm

(continued)

temporarily or permanently, at any time if vaccine production does not meet FDA standards for CGMP, if there are concerns about the safety of the vaccine or if there is evidence of a lack of efficacy.

Licensure

All clinical studies conducted within the IND review process must be close to completion or have been completed before the vaccine sponsor can begin the final vaccine licensure application. In addition, all production techniques must be developed per regulatory guidelines and all manufacturing processes must be standardized. When the vaccine sponsor determines that all of these criteria have been met, the sponsor will apply for a license to manufacture and distribute the vaccine to the public by submitting a Biologics License Application (BLA).

In the BLA, the vaccine sponsor must include: (1) a complete description of all manufacturing and testing methods for the vaccine; (2) results of all laboratory tests performed on a specific number of vaccine production lots that are intended for distribution to the public [this includes the production of at least six large lots of vaccines, each containing tens of thousands of doses, to demonstrate that the manufacturing process is consistent and reliable[6]]; (3) a summary of the results of all clinical studies; and (4) proposed labeling, including the indications, directions and contraindications for use of the vaccine. Information submitted in the BLA must demonstrate compliance with standards for all production materials, facilities, personnel, equipment and packaging. Sponsors must also show that labeling, holding, distribution and record maintenance meet FDA standards.[3]

Scientific review of the BLA is conducted internally by CBER's Vaccines and Related Biological Products Advisory Committee (VRBPAC). This advisory committee reviews the data supporting the safety, purity and potency of the vaccine, and provides recommendations on whether the product should be approved. VRBPAC includes representatives of CBER, a representative from the CDC, professors and leaders from leading US universities and representatives of other organizations.[5,7] During the BLA review, discussions and correspondence between the vaccine sponsor and VRBPAC are ongoing and sometimes outside consultants and advisors are brought in to further review the application.[3]

When the application process is near completion and vaccine production has begun, an announced inspection of the production facility is conducted. This inspection provides an in-depth review of the production facilities, records, process, methods, equipment, quality control procedures and personnel. The committee presents all data and recommendations to CBER, and if CBER determines that the data and information are satisfactory, the vaccine is licensed.[3]

Advisory Committees

After a new vaccine is approved by the FDA, advisory committees made up of immunization experts facilitate the incorporation of the vaccine into public health programs. These advisory committees decide whether to recommend the vaccine for the general population, how the vaccine should be incorporated into established vaccination schedules and how the vaccine should be incorporated into various health service delivery systems. In addition, experts review and update recommendations on existing vaccines and immunization programs.[7] These advisory committees have an even broader mandate than the FDA. Besides evaluating the available safety and immunogenicity data, advisory committees must take into account societal perspectives, the systems in place for delivery of vaccines, cost-effectiveness and cost-benefit

VACCINE ADVISORY COMMITTEE:

Advisory Committee on Immunization Practices (ACIP)
http://www.cdc.gov/nip/acip/default.htm

American Academy of Family Physicians (AAFP)
http://www.aafp.org

American Academy of Pediatrics (AAP) Committee on Infectious Diseases (COID)
http://www.aap.org

National Vaccine Advisory Committee (NVAC)
http://www.cdc.gov/od/nvpo/committee.htm#nvac

Vaccines and Related Biological Products Advisory Committee (VRBPAC)
http://www.fda.gov/cber/advisory/vrbp/vrbpmembers.htm

SURVEILLANCE MECHANISMS:

Institute of Medicine
http://www.iom.edu

Institute of Medicine Immunization Safety Review Committee
http://www.iom.edu/imsafety

National Childhood Vaccine Injury Act
http://www.cdc.gov/nip/vacsafe/default.htm#ncvia

VAERS Information and Reporting Form
http://www.vaers.org

Vaccine Injury Compensation Program
http://www.cdc.gov/nip/vacsafe/default.htm#vicp

Vaccine Injury Table
http://www.bhpr.hrsa.gov/vicp/table.htm

Vaccine Safety Datalink Project
http://www.cdc.gov/nip/vacsafe/default.htm#vsd

REGISTRY INFORMATION:

National Partnership for Immunization
http://www.partnersforimmunization.org/immregistry.html

Immunization Registry Clearinghouse of the National Immunization Program
http://www.cdc.gov/nip/registry/

Every Child by Two
http://www.ecbt.org/immreg.html

All Kids Count
http://www.allkidscount.org

analyses, expert opinion based on similar vaccines and the impact of the new vaccine on child, adolescent and adult immunization schedules.[8]

The following expert advisory committees guide the formulation of government policies:

- **Advisory Committee on Immunization Practices (ACIP)** consists of 15 experts selected by the Secretary of the US Department of Health and Human Services (DHHS) for their expertise in vaccination, infectious diseases and public health. This committee advises the Secretary, the Assistant Secretary for Health and the CDC on the most effective means to prevent vaccine-preventable diseases. ACIP develops written recommendations for the routine administration of vaccines to the public as well as schedules that note the appropriate periodicity, dosage and contraindications for each vaccine.[9]

  The background work leading to vaccination recommendations is done by ACIP working groups. Working groups are composed of ACIP members, representatives of professional societies and other federal agencies and organizations (including industry) with an interest in immunization. Academic researchers and representatives from vaccine manufacturers may serve as consultants to working groups. Working groups consider and summarize data for presentation to the full ACIP.

  The process of developing ACIP recommendations includes: (1) a review of labeling and package inserts for each vaccine; (2) a thorough review of published and unpublished studies on the safety, efficacy, acceptability and effectiveness of the vaccine, with consideration of the relevance, quality and quantity of this data; (3) a cost-effectiveness analysis; (4) a review of the morbidity and mortality associated with the disease both in the general population and in specific risk groups; (5) a review of the recommendations of other groups; and (6) a consideration of the feasibility of incorporating the vaccine into existing child and adult immunization programs. Feasibility issues include acceptability to patients, parents and the community; vaccine distribution and storage; access to vaccine and vaccine administration; impact on health care delivery systems; and social, legal and ethical concerns.

  The final stage of the ACIP vaccine recommendation process is adoption of the working group's recommendations by committee vote. Adoption requires approval by a majority of committee members. In situations where a quorum of members is not present at the meeting or cannot vote because of potential conflicts of interest, *ex officio* members may be authorized to vote.[10] ACIP recommendations are referred to CDC and then to the Secretary of DHHS who may accept or reject the recommendations. If accepted, the recommendations become part of the national immunization policy.

- **National Vaccine Advisory Committee (NVAC)** makes recommendations on vaccine policy, programs and delivery for the entire country. These recommendations are given to the Director of the National Vaccine Program Office (NVPO) of the US Department of Health and Human Services (DHHS) who then reports all proceedings to the US Surgeon General. NVPO was established by DHHS to achieve optimal prevention of human infectious diseases through immunization and to achieve optimal prevention of adverse events associated with vaccine use.[11] NVPO helps to coordinate the vaccine efforts of the US Public Health Service and NVPO's Interagency Vaccine Group (IAVG).

- **Office of Emergency Preparedness (OEP)** is located within DHHS and is responsible for managing and coordinating federal health, medical and health-related social services and recovery from major emergencies and federally declared disasters such as natural disasters, technological disasters, major transportation accidents and terrorism. This agency plays a major role in the development of policies for the use and distribution of vaccines that help prevent diseases caused by certain potential bioterrorism agents.

- **Advisory Commission on Childhood Vaccines (ACCV)** gives the Secretary of Health and Human Services advice regarding the National Vaccine Injury Compensation Program (VICP) (see page 24). Such advice includes recommendations on VICP implementation, on changes to the list of adverse events for which this program provides compensation, on the provision and use of childhood vaccines with few or no significant adverse reactions, on obtaining and using credible data on the frequency and severity of adverse reactions associated with childhood vaccines and on research to be conducted.

The following professional organizations provide information and perspectives during the process of federal vaccine policy development and guide the implementation of these policies by conveying them to their constituents:

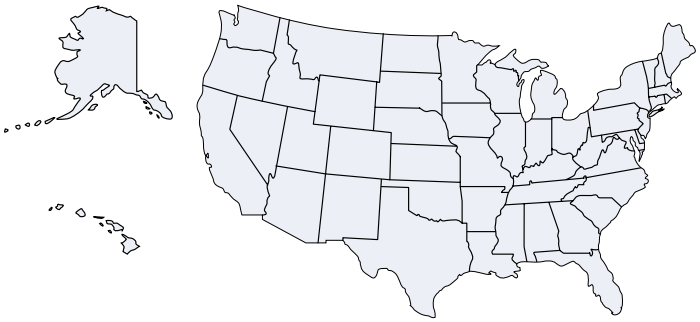
- **American Academy of Pediatrics (AAP),** a professional organization of pediatricians, has established the Committee on Infectious Diseases (COID) that monitors developments in the prevention, diagnosis and treatment of infectious diseases and reports these to AAP members with pertinent recommendations. The Committee regularly updates the Red Book: Report of the Committee on Infectious Diseases and develops and reviews policy recommendations on the use of vaccines.[12]

- **American Academy of Family Physicians (AAFP),** a professional organization for doctors specializing in family medicine, provides recommendations and policy statements to its members on vaccine use and delivery.[13]

Vaccine Information Statements

Vaccine Information Statements (VISs) are information sheets on the recommended vaccines that are produced by the Centers for Disease Control and Prevention (CDC). Federal law requires that this information be given to vaccine recipients, their parents or their legal representatives whenever certain vaccinations are given (prior to each dose of these vaccines). VISs provide general information about a particular vaccine and the diseases that the vaccine helps to prevent and explain both the benefits and risks of the vaccine. VISs are available for the following vaccines: diphtheria, tetanus, acellular pertussis (DTaP); hepatitis A; hepatitis B; *Haemophilus influenzae* type b (Hib); influenza; measles, mumps, rubella (MMR); meningococcal; pneumococcal conjugate; pneumococcal polysaccharide; tetanus/diphtheria; varicella; and anthrax. These forms are now available in over 26 different languages and can be downloaded from the Immunization Action Coalition Web site at www.immunize.org/vis.

State Requirements



Individual states are responsible for implementing all vaccine requirements, including school immunization requirements. In 1809, Massachusetts passed the first immunization law, requiring its population to be vaccinated against smallpox.[14] States' rights to pass compulsory immunization laws were confirmed by the Supreme Court in 1905 and upheld in 1922 in a case involving required vaccination for school entry. Modern school immunization laws began with efforts to eliminate measles in the US in the 1960s and 1970s.[14] The usefulness of these laws was revealed by early data showing a 40% to 51% lower rate of measles in states with school immunization laws compared with those without such laws.[15] Immunization mandates during measles outbreaks in Alaska in 1976[16] and in Los Angeles in 1977[17] proved to be very effective in preventing and eliminating the spread of measles.

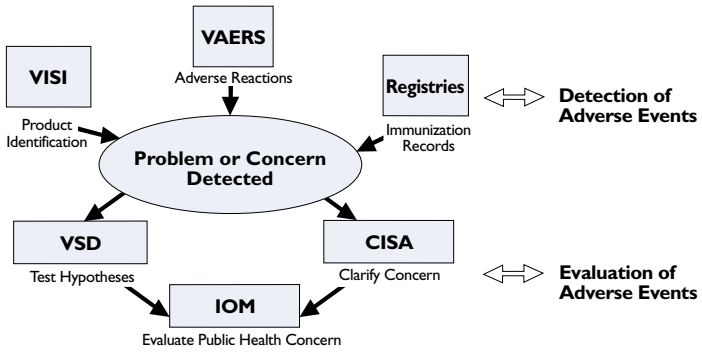
Today, states make decisions based on the recommendations of the vaccine advisory committees, recognizing the need to prevent disease epidemics and to reduce disease burdens. State mandates exist for childhood and adolescent immunizations but do not include adult immunizations. All 50 states have both school immunization laws as well as medical criteria for exemption from mandated immunizations. Forty-eight states allow exemptions to immunization based on religious beliefs, and 15 states also allow for philosophical exemptions from mandated immunizations.[18]

Vaccine Financing

Programs have been established to finance the purchase of vaccines for low-income, uninsured and underinsured children. Currently, almost 60% of pediatric vaccines are purchased either by the federal government or by state and local governments through documented federal contracts. Most federally purchased vaccines are supplied through the Vaccines for Children (VFC) program, providing free vaccines for administration to eligible persons from birth through 18 years of age. Funds are also appropriated under a grant program established by Section 317 of the Public Health Service Act. These funds are distributed by CDC to state and local immunization programs to support vaccination in public clinics and, in some states, by private providers. Costs of influenza and pneumococcal vaccination for persons over 65 years old are covered by Medicare part B.[19]

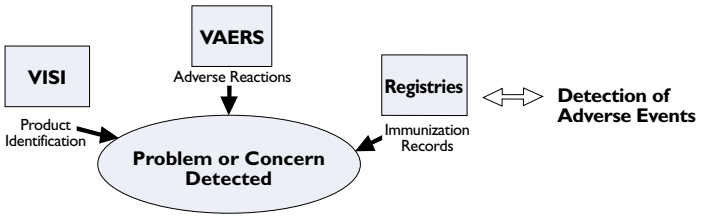
Vaccine Surveillance Mechanisms

Government monitoring and interest in vaccine use does not stop once a vaccine is licensed and is made available to the general public. National detection and evaluation systems are in place to continually assess the safety and efficacy of vaccines that are widely used in the US.



Detection of Adverse Events

At least three mechanisms exist within the immunization system to help detect adverse events in a timely and accurate fashion.



(1) Vaccine Identification Standards Initiative (VISI)

Currently being incorporated into the manufacturing process of vaccines, the Vaccine Identification Standards Initiative (VISI) requires the placing of a bar-coded sticker on each vaccine. Health professionals can peel off the sticker and place it on the immunization record of the person being vaccinated, allowing health officials to directly link reports of adverse events to specific products and lots while increasing the accuracy and availability of information contained in individual immunization records.

(2) Immunization Registries

Immunization registries are confidential, computerized systems that contain information about an individual's immunization record and their compliance with the vaccine schedules. Besides identifying vaccine coverage, registries help programs assess safety by confirming who has received which vaccine as well as where and when the vaccine was administered. Registries can also generate reminder or recall notices to patients when revaccination is needed or when new vaccines are introduced.

Cost analyses have shown that registries can save enormous amounts of money.[20] Sixteen vaccination registry projects have estimated costs for the average child to participate in a registry to be $3.91 or $78 million for all children aged 0-5. But once established nationwide, registries would save health care and education systems $280 million annually.[21]

(3) Vaccine Adverse Event Reporting System (VAERS)

Adverse events are undesirable experiences occurring after immunization that may or may not be related to the vaccine.

Adverse events can range from mild reactions such as pain at the vaccine injection site to more severe reactions such as seizures. Although most vaccine manufacturers encourage the reporting of adverse events to them, Congress recognized the importance of establishing an independent reporting program to ensure scientific independence when evaluating vaccine safety. Therefore, in 1986, Congress created the Vaccine Adverse Event Reporting System (VAERS) under the National Childhood Vaccine Injury Act[22] to serve as the mechanism by which information about adverse events following immunization may be reported, analyzed and made available to the public.[23] VAERS replaced the Monitoring System for Adverse Events Following Immunization (MSAEFI) established in 1978 by the Centers for Disease Control and Prevention (CDC), which required the distribution of an information leaflet to all recipients of vaccines. The leaflet contained a statement requesting that vaccine recipients notify a doctor that they had recently been vaccinated should they require medical care within four weeks of vaccination. VAERS expands upon this program by accepting reports directly from lay persons, distributing report forms to all physicians, providing a list of events mandated for reporting and establishing a 24-hour toll-free help line.[24]

In addition, the National Childhood Vaccine Injury Act mandated that before administering each vaccine, health care providers must give each person who is to be vaccinated or their guardian a copy of the corresponding vaccine information statement (VIS). Available since April 1992, these statements outline the benefits and risks of vaccination and give information on how to report the occurrence of an adverse event to VAERS.[25]

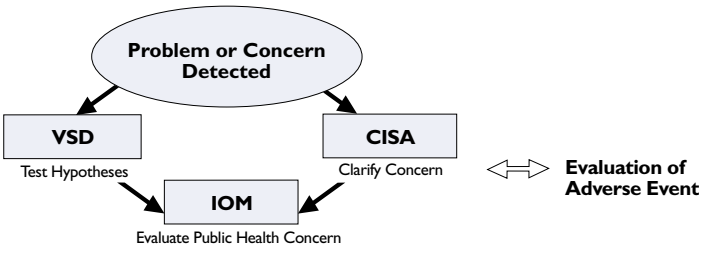
VAERS serves both as a national registry of adverse events following immunizations and as a tool used by the Food and Drug Administration (FDA) and CDC to generate hypotheses regarding potential associations between mild and serious events and vaccine administration. VAERS attempts to detect previously unrecognized vaccine-related reactions, unusual increases in previously reported events, pre-existing conditions that may be associated with certain reactions and contraindicate additional doses of the vaccine as well as to identify specific vaccine lots associated with reported events.[26] Both the FDA and CDC review data reported to VAERS. The FDA surveys individual reports to update product labeling, to perform comprehensive review of recently licensed vaccines, and to monitor trends for individual vaccine manufacturers and lots. The CDC reviews collective reports to detect and analyze epidemiological trends and associations.[27]

To accomplish its objectives, VAERS report forms are mailed directly to approximately 200,000 primary care physicians, emergency room directors and state health departments each year. A report form can also be found in the Physician's Desk Reference, in the American Academy of Pediatrics' Red Book: Report of the Committee on Infectious Diseases and can be accessed through the Internet (see Web Resources). Reporters to VAERS receive letters acknowledging that their report was received. While reporters are generally encouraged to send in reports as soon as possible, vaccine manufacturers are required to send in serious adverse event reports within 15 days of receiving those reports.[26]

The strengths of VAERS lie in its national scope, its timeliness in gathering information about adverse events and its relatively cost-effective implementation. Because VAERS is a passive or voluntary reporting system, the database is subject to under-reporting, biased reporting, inadequate report quality, differences in reporting rates between the public and private sector and increased reporting when a vaccine is first licensed, or following the appearance of media stories questioning the safety or importance of a vaccine, etc.[27] Interpretation of VAERS data is also difficult due to the mixing of multiple exposures and outcomes, difficulty in detecting new and changing adverse events and mixing of potentially causal and coincidental events. The lack of denominators, i.e., information on the total number of people receiving the vaccine of interest, and control groups creates difficulty in applying information from VAERS to the general population. Although unable to address potential vaccine-adverse event causality, the usefulness of VAERS is due to the ability to use the data to propose hypotheses about potential causal relationships that can be tested and verified by other mechanisms.[28]

VAERS data have been extensively utilized. The Institute of Medicine (IOM) Vaccine Safety Committee used VAERS to assess various relationships between childhood vaccines and adverse events in 1994.[29] The Advisory Committee on Immunization Practices (ACIP) has documented possible adverse events and adverse events related to vaccination and developed recommendations for precautions and contraindications to vaccination through review of VAERS data. CDC and FDA have used VAERS to screen for and detect previously unrecognized reactions to current and future vaccines. For example, investigations of VAERS reports by the FDA have shown that the hepatitis B vaccine is safe for use in infants.[30] Similar investigations have been conducted for hepatitis A[31] and varicella vaccines.[32] VAERS data were used to compare the safety record for diphtheria, tetanus, acellular pertussis (DTaP) vaccine[33] and inactivated poliovirus (IPV) vaccine[34] with the vaccines they replaced (diphtheria, pertussis, whole cellular pertussis vaccine and oral poliovirus vaccine, respectively). VAERS detected influenza vaccine-associated increased rates of Guillain-Barré syndrome from 1992-1993 to 1993-1994,[35] and increased rates of intussusception associated with the rotavirus vaccine in 1999.[36] These surveillance data led to further research into potential associations between each vaccine and the corresponding reported diseases and resulted in the withdrawal from use of the rotavirus vaccine.[37,38]

Evaluation of Adverse Events



The Vaccine Safety Datalink Project (VSD) and the Clinical Immunization Safety Assessment (CISA) Centers are two systems created to evaluate and clarify hypotheses generated from information gathered from the three reporting mechanisms described above.[28] Committees of the IOM also review these hypotheses as well as various immunization research studies to provide research and policy recommendations.

(1) Vaccine Safety Datalink (VSD) Project

This collaboration between CDC and several health maintenance organizations (HMOs) began in 1991 and is aimed at testing the hypotheses raised by adverse events reports. Today, over 7.5 million people (approximately 2.5% of the United States population) are involved through eight participating HMOs. The VSD database is able to combine information on patient vaccination records, health outcomes (from hospital, emergency room and out-patient department records) and patient characteristics (birth certificate and census information) to test such hypotheses. Additional information on socioeconomic status is obtained by linking the zip codes and street addresses of the patients with their respective census tract blocks.

Initially, data were only obtained for infants and children up to six years of age, but now VSD incorporates information on older children, adolescents and adults. To maintain patient confidentiality, participants have unique identification numbers that can be used to link data on their medical services within the HMO. Each site sends its encoded data to the CDC for merging and analysis. Routine data quality checks for each of the databases are conducted periodically using a random 2% sample of the study population to review the automated vaccination and diagnostic data entry.

The VSD acts as a large cohort for post-licensure surveillance and is useful for accurate risk-benefit assessment by both the public and policymakers.[39] The project provides information to calculate incidence rates, attributable risks and background rates of illness in the absence of vaccination in a more timely and efficient manner than an ad hoc epidemiological study. Follow-up diagnosis validation is also possible for specific adverse events. However, only short-term follow-up information may be available for persons who have either just entered or have left one of the participating HMOs. The VSD population has become more geographically diverse and representative of the US population as a whole with each addition of a new HMO. However, the population remains skewed towards the middle class and few unvaccinated controls are available because of the high vaccination coverage attained within participating HMOs. Some patient characteristic information can take about one year to obtain and prepare for incorporation, making the project more costly than basic passive surveillance. Despite the large number of persons included in this surveillance system, VSD is not sufficiently large or diverse to test certain hypotheses regarding very rare events (such as the postulated relationship between the influenza vaccine and Guillain-Barré syndrome or the safety concern of vaccines containing thimerosal). Studies of adverse events with delayed onset, e.g. autism, are difficult for VSD,[28] and inferences that can be made about vaccine-disease causality are limited.

VSD studies have been published on such topics as vaccine coverage, disease incidence, methodology, vaccine safety and cost-effectiveness. Completed studies have informed the public about immunization issues in the US such as the recommended age to administer the second dose of measles, mumps, rubella (MMR) vaccine and revaccination with pneumococcal polysaccharide vaccine, and have increased public knowledge about proposed associations between vaccines and diseases such as autism, diabetes and inflammatory bowel disease.[39–42] Both the number and the size of the VSD studies continue to grow. This monitoring system is vital in order to observe a vaccine's effect on a large population and to maintain public confidence in vaccines.[39]

(2) Clinical Immunization Safety Assessment (CISA) Centers

The Clinical Immunization Safety Assessment (CISA) network, funded in October of 2001, is comprised of academic centers with clinical expertise in adverse events following immunization. In partnership with the Centers for Disease Control and Prevention (CDC), the network seeks to improve the scientific understanding of vaccine safety at the individual "patient" level. The purpose of CISA centers is to serve as an intermediate step between passive reporting of individual cases of adverse events with no or minimal follow-up and more rigorous vaccine safety epidemiological investigations.

Once fully established, CISA center staff will systematically evaluate cases of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS) or referred to them by health care providers. Selected cases will undergo enhanced follow up and targeted clinical evaluation to better understand the mechanism(s) and risk factors for their particular adverse event. The results of these evaluations will be used to develop clinical evaluation protocols or patient management guidelines that can be used by all health care providers.[28] The first group of CISA centers was funded in October 2001 and includes Johns Hopkins University partnering with specialists at the University of Maryland, in Baltimore; Northern California Kaiser with collaborators at Stanford University in San Francisco, California; Vanderbilt University in Nashville, Tennessee; Boston University Medical Center in Boston, Massachusetts; and Columbia Presbyterian Hospital in New York City, New York.

(3) Institute of Medicine (IOM)

Funded by Congress, the mission of this independent body is to advance and disseminate scientific knowledge to improve human health. The IOM provides objective, timely, authoritative information and advice to the federal government concerning health and safety policy. IOM studies have been conducted on vaccine safety, childhood immunization, immunization policy, vaccines and the military, and vaccine research and development.[43] In order to evaluate current immunization programs and vaccine recommendations, the National Childhood Vaccine Injury Act of 1986 (see Vaccine Injury Compensation Program below) established a committee of the IOM to comprehensively review the medical literature on vaccine-related adverse events.[7]

In 1991 and 1993, two reports from this committee showed that inadequate or no data existed to either accept or reject 50 (66%) of the 76 potential vaccine adverse events that were evaluated. The study stated that "many gaps" exist in both current knowledge and research capacity. These gaps included inadequate understanding of the relevant biological mechanisms, insufficient/inconsistent information from case reports, inadequate size or follow-up of many epidemiologic studies, limited surveillance to assess causation and few experimental studies performed to assess the causes of adverse events.[29]

Recently, the CDC and the National Institutes of Health (NIH) commissioned the IOM to establish an Immunization Safety Review Committee, a body of independent experts charged with reviewing hypotheses regarding vaccine safety. This Committee will meet three times each year over the course of its three-year study period (2001-2004). Each meeting will focus on specific hypothesized concerns about vaccine safety. A report assessing biologic plausibility and identifying competing hypotheses and available scientific evidence is to be issued following each meeting. When appropriate, the committee will make specific recommendations to policy-makers.[44]

The Committee held its first meeting in January, 2001 and has since evaluated several vaccine safety issues. All issues evaluated by this committee have been addressed in the *Vaccine Safety Issues* section. Other Committee information, including its schedule, is available through the IOM Immunization Safety Review Committee Web site (see Web Resources).

Vaccine Injury Compensation Program (VICP)

Established by Congress under the 1986 National Childhood Vaccine Injury Act, this program provides compensation to children who have been injured from a vaccine administered as part of the routine childhood immunization schedule. Funding for VICP comes from excise taxes imposed on vaccine manufacturers. Prior to this program, drug manufacturers and health care providers paid millions of dollars to the families of children allegedly injured by adverse events attributed to childhood immunizations. Because of escalating costs associated with litigation and settlements, the cost of immunizations to providers increased dramatically, and some producers withdrew from the market to reduce liability costs. To help solve this problem, Congress established the VICP no-fault compensation system that went into effect on October 1, 1988.

In order to receive compensation from this program, persons must file a claim against the Secretary of the US Department of Health and Human Services (DHHS) within three years of injury or two years of death. Persons injured before the effective date of the Act may pursue compensation through state law or through this federal program. Persons filing claims to VICP may not sue either the manufacturer or anyone involved with vaccine administration until the claim against DHHS has been resolved. Claimants have 60 days to accept—or reject—a judgement or award. The decision is irrevocable. If claimants accept compensation under the Act, they will not be able to pursue further compensation. However, claimants who reject a judgement can bring civil action for damages against the manufacturer of the vaccine, the person who administered the vaccine, or both; the findings of the VICP are not admissible in the civil action.

This federal program qualifies more vaccine-injured children for compensation than would have been possible under the former tort system. State civil action requires that plaintiffs show both that the wrong actually caused the injury and that the party against whom they are seeking compensation did something wrong. More vaccine-injured children qualify for compensation under VICP because claimants must only show that they were injured by the vaccine to succeed in their claim against DHHS. Injury criteria acceptable for compensation are detailed on the Vaccine Injury Table (see Web Resources). Children whose injuries do not appear in the Vaccine Injury Table may also recover damages under the Act, but only if they can prove that the immunization actually caused their injuries. The less complex set of requirements is a benefit for claimants not only because it makes it much more likely that they will qualify for compensation but also because it streamlines the proceedings, requiring less legal involvement and permitting more rapid compensation.

Claimants are entitled to damages limited to the actual costs of care for treatment and rehabilitation not covered by public or private insurance. Monetary caps limit damages for pain and suffering and for wrongful death to $250,000 each. Finally, certain types of damages, including punitive damages and so-called derivative claims by family members for loss of companionship, are not permitted under the Act. Claimants may recover attorneys' fees under the Act even when they are not awarded compensation so long as their claim was "brought in good faith and there was a reasonable basis for the claim." [45,46]

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VACCINES

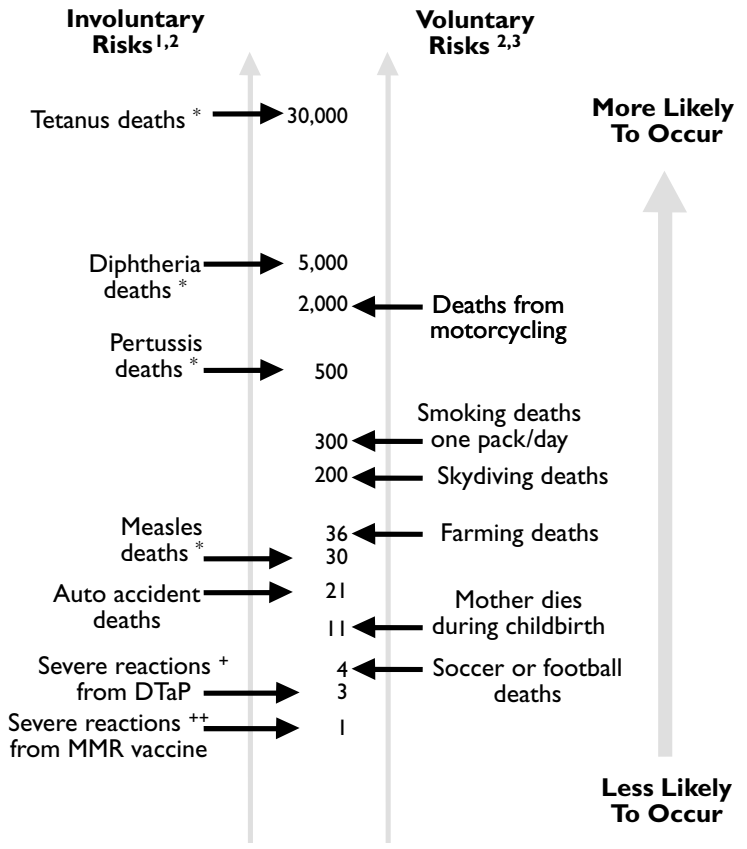
VACCINES

Safety Assessment

Most dictionaries define safety as freedom from harm. So in order for something to be 100% safe, it would have to be completely devoid of any and all chance of harm. As the following examples indicate, nothing we do nor experience fits this qualification. We can slip and fall as we get out of bed, become ill or choke on our food as we eat, get hit by a car as we cross the street, turn an ankle or bump into something as we walk or inhale dangerous chemicals, smoke or viruses as we breathe. Therefore, we must analyze the risks and benefits of a situation in order to decide the course of action we will take. Although the risks described exist, they need to be balanced against the benefits of taking each risk. We must get up out of bed in order to move on with our day, eat food to nourish ourselves, cross the street to continue our journey, walk to move forward and breathe to stay alive.

Likelihood of Death or Serious Injury Associated with Disease, Vaccination and Various Activities

(Values are expressed as the number of affected persons per 100,000 people at risk each year in the United States.)



* Risk of death from this disease once disease has been contracted.

\+ Includes breathing difficulty and shock and severe brain reactions such as long seizures, coma or lowered consciousness.

++ Includes temporary bleeding problems, seizures related to high fever, lowered consciousness or coma.

Physicians, public health officials and individuals share an interest in understanding the health and safety implications associated with vaccine usage. As noted in the section *Importance of Immunizations*, vaccines play an significant role in protecting both individuals and the community at large from infectious diseases. In the absence of such protection, diseases such as measles, mumps, polio and hepatitis can cause injury and death. This is illustrated in the accompanying figure. For example, in the absence of a vaccine against tetanus, out of every 100,000 persons in the US infected

GLOSSARY TERMS

Adverse events
Advisory Committee on Immunization Practices
Anthrax
Cases
Diphtheria
Disease
Encephalitis
Measles
Mumps
Pertussis
Risk
Rubella
Smallpox
Tetanus
Vaccine
Virus

ACRONYMS

DTaP	Diphtheria, tetanus, acellular pertussis vaccine
MMR	Measles, mumps, rubella
NIH	National Institutes of Health

WEB RESOURCES

Centers for Disease Control and Prevention (CDC), National Immunization Program
http://www.cdc.gov/nip/vacsafe/#risk

Harvard Center for Risk Analysis
http://www.hcra.harvard.edu

Johns Hopkins School of Public Health, Risk Sciences and Public Policy Institute
http://www.jhsph.edu/research/centers/rsppi

Society for Risk Analysis
http://www.sra.org

with the tetanus-causing bacterium, 30,000 would die. Similarly, if there was no diphtheria vaccine, 5,000 out of every 100,000 infected children would die on an annual basis. In contrast, out of every 100,000 people who smoke one pack of cigarettes a day, 300 deaths would be expected each year.

As pointed out in the above diagram, absolute safety cannot be guaranteed; everything carries some risk. The section *Federal Regulation, Surveillance and Evaluation of Vaccines* describes the strong commitment of the government, researchers, public health officials, advisory committees and vaccine manufacturers to provide the public with the safest vaccines possible.

Despite these efforts, because no two people are identical, different persons may vary in how they will respond to a vaccine. Most will quickly develop an effective, protective immunity to the disease agent without complications, some (a very small minority) will not develop immunity for a variety of medical reasons and rarely, responders and non-responders will develop a severe adverse reaction. Current scientific knowledge cannot identify how individuals will react to a vaccine.

The diagram above places the health risks associated with vaccinating or not vaccinating in context with the risk of injury or death associated with other activities. One in 100,000 children given the MMR vaccine will have a serious adverse reaction; 30 in 100,000 unvaccinated children who develop measles will die of complications brought on by the infection.

Recent events provide an example of how fear can alter a person's ability to make rational decisions, weighing both the benefits of acting against the risks of not. Following the anthrax attacks in October and November 2001, heightened concern has been raised across the country about the potential use of smallpox virus as a bioterrorism weapon. As a result, a National Institutes of Health (NIH) study was launched in October 2001 to determine if existing smallpox vaccine stocks could be diluted to be used for more people. In addition, US officials signed a $428 million contract with Acambis and Baxter International to fast-track delivery of 155 million smallpox vaccine doses by the end of 2002.[4] Continued speculation that terrorists might use smallpox virus as a weapon has resulted in mounting pressure in the US to provide widespread, or even universal, smallpox vaccination. A poll in May 2002 found that 59% of Americans would get a smallpox vaccination if the vaccine were made available.[5] And, during recent Congressional hearings, Congress members' views often echoed that of US Senator Arlen Specter (R-PA) who said that it is just "common sense" to make smallpox vaccine available to everyone who wants it.[6]

But how much sense does it really make? Smallpox has not been seen since 1977 and has been eradicated worldwide. Other than through a criminal act, the risk of developing smallpox is zero. But the risk of serious and life-threatening adverse events is greater with the smallpox vaccine than with any other recommended vaccine.[7] Approximately one in every 300,000 persons who receive a dose of this vaccine will develop encephalitis, which can lead to permanent neurological damage; and between one and three in every million persons who receive the vaccine will die. If the smallpox vaccine was made available to the general public, approximately 25% of the US population would be excluded from receiving the vaccine because they would be at high risk of developing adverse events or because they are close contacts of a high-risk individual. After excluding this group of people, a recent study found that vaccination of all persons one to 65 years of age in the US would result in approximately 4,600 serious adverse events and 285 deaths.[7]

At the June 2002 Advisory Committee on Immunization Practices (ACIP) meeting, members decided that under current circumstances that include no cases of confirmed smallpox and a low risk of a bioterrorism attack using smallpox, vaccination should not be recommended for the general population, as the potential benefits of vaccination would not outweigh the risks of vaccine adverse reactions. However, smallpox vaccination is recommended for persons pre-designated by the appropriate bioterrorism and public health authorities to conduct investigation and follow-up of initial smallpox cases that would necessitate direct patient contact.[6]

The example of smallpox demonstrates how widespread fears and misinterpretation can cloud one's judgement about the necessity and safety of vaccines. For this reason, public health officials scrutinize in great detail all of the risks and benefits before they make decisions about the licensure and use of vaccines for the general population. Providing the public with safe vaccines is the point of the testing, evaluation and review that each vaccine undergoes before licensing, and why surveillance and other follow-up studies continue long after the vaccine is marketed. Scientists in government, industry and academic laboratories are committed to assuring and improving the safety of current vaccines, and making the next generation of vaccines even safer.

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DIPHTHERIA, TETANUS, ACELLULAR PERTUSSIS (DTaP) VACCINE

General Disease Information

Diphtheria is a serious respiratory disease caused by the bacterium *Corynebacterium diphtheriae*. These bacteria infect the throat, tonsils, skin and nose and can cause a sore throat and cough. In some cases, a characteristic thin gray membrane coats the tonsils and throat and may block the patient's airway. If diphtheria is not treated, the disease can lead to pneumonia, heart failure, paralysis and death.[1, 2]

Tetanus, a disease of the nervous system, is caused by the bacterium *Clostridium tetani*, which can be found in dirt, gravel and on objects associated with these such as rusty metal. The bacteria enter the body through a break in the skin and release a toxin, or poison, that causes the muscles to spasm. The toxin first attacks jaw muscles and may cause them to "lock" (this disease characteristic has led to tetanus also being referred to as lockjaw). Tetanus can go on to affect other muscles, leading to abdominal rigidity and generalized painful muscle spasms; death may result.[1-3]

Pertussis, or whooping cough, is a highly contagious respiratory disease caused by the bacterium *Bordetella pertussis*. The disease can last for up to two months and produces a severe "barking" cough followed by an inspiratory "whoop" lasting up to two months and often occurring in spasms that can make it difficult to eat, drink or sleep. Complications of pertussis can result in pneumonia, encephalopathy, seizures and death. Young infants are at the greatest risk for acquiring pertussis and for pertussis-associated complications.[1-3]

Benefits from Vaccination

Completion of the full DTaP vaccine series is over 95% effective in preventing children from contracting the diseases of diphtheria, tetanus and pertussis. Prior to the availability of vaccine, the number of cases and deaths for diphtheria, tetanus and pertussis were significant. More than 175,000 cases of diphtheria, 1,300 cases of tetanus and 140,000 cases of pertussis were reported per year before the introduction of the vaccine.[4] Up to 10% of diphtheria cases[5], 11% of tetanus cases[6] and 0.2% of pertussis cases[6] die from the respective disease. In 2000, 7,867 cases of pertussis, 35 cases of tetanus and one case of diphtheria were reported in the United States.[4]

Risk of Vaccine Adverse Events

Most children experience no adverse reactions to DTaP. Some 1% to 5% of children vaccinated with DTaP develop mild adverse events such as injection site tenderness, swelling and redness as well as fretfulness, drowsiness, vomiting and minor fevers. About 1% of children experience moderate reactions such as prolonged crying, high fever, seizure or the child becomes limp, pale or less alert. Less than three serious adverse events (breathing difficulty and shock, prolonged seizure, coma or lowered consciousness) are reported per 100,000 children vaccinated.[3]

Cost-Benefit Analysis

An economic analysis of diphtheria, tetanus, pertussis vaccine use in the United States has calculated a societal net savings of over $22 million for DTaP and $22.62 million for diphtheria, tetanus, whole cell pertussis vaccine (DTP). The benefits of DTaP exceeded the costs by 27:1 for indirect costs and 9:1 for direct health care costs.[7]

Safety Studies

- When DTP was first licensed in the late 1940s, it contained whole killed pertussis organisms. Following the release of two reports by the Institute of Medicine (IOM), which found evidence that supported a causal relationship between DTP immunization and rare severe adverse events,[8] a new vaccine was developed. The pertussis

GLOSSARY TERMS

Adverse events
Advisory Committee on Immunization Practices
Bacteria
Booster
Bordetella pertussis
Cases
Clostridium tetani
Coma
Combination vaccine
Corynebacterium diphtheriae
Diphtheria
Disease
Encephalopathy
Heart failure
Immunization
Pertussis
Pneumonia
Protein
Risk
Seizure
Spasm
Sudden Infant Death Syndrome
Tetanus
Tonsil
Toxin
Vaccine
Whooping cough

ACRONYMS

DTaP	Diphtheria, tetanus, acellular pertussis vaccine
DTP	Diphtheria, tetanus, whole cell pertussis vaccine
IOM	Institute of Medicine
SIDS	Sudden Infant Death Syndrome
VAERS	Vaccine Adverse Events Reporting System

WEB RESOURCES

DIPHTHERIA:

National Partnership for Immunization
http://www.partnersforimmunization.org/diphtheria.html

Centers for Disease Control and Prevention's *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)*
http://www.cdc.gov/nip/publications/pink/dip.pdf

National Network for Immunization Information
http://www.immunizationinfo.org/database/index.cfm

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/each_vaccine2.shtml#name01

Immunization Action Coalition
http://www.immunize.org/diphtheria

TETANUS:

National Partnership for Immunization
http://www.partnersforimmunization.org/diphtheria.html

Centers for Disease Control and Prevention's *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)*
http://www.cdc.gov/nip/publications/pink/tetanus.pdf

National Network for Immunization Information
http://www.immunizationinfo.org/database/index.cfm

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/each_vaccine2.shtml#name02

Immunization Action Coalition
http://www.immunize.org/tetanus

PERTUSSIS:

National Partnership for Immunization
http://www.partnersforimmunization.org/diphtheria.html#pertussis

(continued)

component of this new acellular vaccine (DTaP) contained only the specific parts of pertussis bacteria necessary to establish protective immunity. Pre- and post-licensure studies have shown that adverse events occurred less frequently among infants vaccinated with acellular pertussis combination vaccine (DTaP) than among those vaccinated with whole-cell pertussis combination vaccine (DTP).[1, 5, 7, 9-17]

- A study involving 22,505 subjects who were given a total of 67,000 doses of DTaP found that incidences of sudden infant death syndrome (SIDS), infantile spasms and seizures without fever following vaccination did not exceed those estimated for the general population.[18]
- An analysis of all VAERS data from the first two years of DTaP use found that the annual number of reported adverse events following vaccination with all pertussis-containing vaccines declined after the introduction of DTaP. No clear DTaP safety concerns were identified during this period.[9]
- Review of post-licensure Vaccine Adverse Event Reporting System (VAERS) reports after five million doses of DTaP had been distributed showed that all reported adverse events, seizures and hospitalizations for DTaP were approximately one-third of those reported to be associated with whole-cell pertussis-containing vaccines.[19]

Centers for Disease Control and Prevention's *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)*
http://www.cdc.gov/nip/publications/pink/pert.pdf

National Network for Immunization Information
http://www.immunizationinfo.org/database/index.cfm

Vaccine Education Center at the Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/each_vaccine2.shtml#name03

Immunization Action Coalition
http://www.immunize.org/pertussis

DTaP VACCINE:

National Partnership for Immunization
http://www.partnersforimmunization.org/diphtheria.html#pertussis

Recommendations of the Advisory Committee on Immunization Practices (ACIP)
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4913al.htm
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5102al.htm

DTaP Vaccine Information Statement
http://www.cdc.gov/nip/publications/vis/vis-dtp.pdf

Tetanus-Diphtheria Vaccine Information Statement
http://www.cdc.gov/nip/publications/vis/vis-td.pdf

VACCINE MANUFACTURERS:

Aventis Pasteur
http://www.us.aventispasteur.com/vaccines/tetanus/main.htm

GlaxoSmithKline
http://www.worldwidevaccines.com/public/diseas/diphth.toc.asp

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HAEMOPHILUS INFLUENZAE TYPE B (HIB) VACCINE

General Disease Information

The bacteria *Haemophilus influenzae* type b (Hib) can cause a severe infection in infants and young children. Invasive disease caused by these bacteria can spread to many organ systems and cause meningitis, epiglottitis, pneumonia, arthritis and cellulitis, and is spread by contact with secretions, coughing and sneezing. Invasive Hib disease is uncommon beyond five years of age, presumably because the immune system matures with age thus resulting in greater levels of protection from this disease.[1, 2]

Benefits from Vaccination

Vaccination prevents children from contracting meningitis, epiglottitis, pneumonia, arthritis and skin infections. Because Hib bacteria can live in the throats of healthy people, the potential for unprotected children to contract this disease is high.[3] Before the introduction of the vaccine, about 20,000 cases occurred annually in the United States, primarily among children younger than five years of age (approximately one in 200 children in this age group).[4] Hib was also the leading cause of bacterial meningitis and other invasive bacterial disease among children less than five years old. Five percent of children who developed Hib meningitis died, and 10% to 30% of survivors had permanent brain damage.[5]

Surveillance has shown that the introduction of Hib vaccine in the United States coincided with steep declines in Hib disease in infants less than one year old. Public health officials have largely attributed the rapid reduction in the number of disease cases to the vaccine's ability to reduce carriage of Hib among the vaccinated population, which likely reduced exposure and infection even in those persons who were not immunized.[6, 7] The Centers for Disease Control and Prevention (CDC) data suggest that the number of cases of disease that have occurred since the vaccine was first licensed has significantly decreased. In 2000, 1,398 such cases were reported.[5, 8]

This trend has also been seen in other countries. In Finland, large-scale immunization against Hib began in 1986 and, since 1988, Hib has disappeared, eliminating one-third of Finland's cases of childhood septic arthritis. This resulted in a reduction in the amount, cost and variety of medication needed to treat children with this disease.[9]

Risk of Vaccine Adverse Events

More than 70% of children who receive this vaccine will experience no adverse events.[3] Mild reactions that have been reported include injection site tenderness, swelling and redness as well as mild to moderate fever.[3] Hib vaccine is not known to cause serious adverse events.[10]

Safety Studies

- The safety and immunogenicity of the vaccine were evaluated in a study of 61,080 children ages six weeks to six months in the Kaiser Permanente Medical Care Program of Northern California. The rate of sudden infant death syndrome (SIDS) following vaccine administration did not differ significantly from that of unvaccinated children of the same ages and was lower than that observed for the Kaiser Permanente Medical Care Program as a whole.[11]
- The Institute of Medicine (IOM) reviewed the safety of many childhood vaccines and did not find any serious adverse events linked to Hib vaccines.[12, 13]

GLOSSARY TERMS

Adverse events
Advisory Committee on Immunization Practices
Arthritis
Bacteria
Bacterial meningitis
Cases
Cellulitis
Disease
Epiglottitis
Haemophilus influenzae type b
Hib vaccine
Immunization
Influenza
Invasive
Pneumonia
Risk
Septic arthritis
Sudden Infant Death Syndrome
Vaccine

ACRONYMS

CDC	Centers for Disease Control and Prevention
Hib	*Haemophilus influenzae* type b
IOM	Institute of Medicine
SIDS	Sudden Infant Death Syndrome

WEB RESOURCES

HIB VACCINE:

National Partnership for Immunization
http://www.partnersforimmunization.org/haemophilus.html

Centers for Disease Control and Prevention's *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)*
http://www.cdc.gov/nip/publications/pink/hib.pdf

National Network for Immunization Information
http://www.immunizationinfo.org/database/index.cfm

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/each_vaccine2.shtml#name05

Immunization Action Coalition
http://www.immunize.org/hib

Recommendations of the Advisory Committee on Immunization Practices (ACIP)
http://www.cdc.gov/mmwr/preview/mmwrhtml/00022926.htm

Vaccine Information Statement
http://www.cdc.gov/nip/publications/vis/vis-hib.pdf

VACCINE MANUFACTURERS:

Aventis Pasteur
http://www.us.aventispasteur.com/vaccines/hib/main.htm

Merck Vaccine Division
http://www.merckshardpdohme.com/disease/preventable/hib

Wyeth Vaccines
http://www.vaccineworld.com

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HEPATITIS A VACCINE

General Disease Information

Hepatitis A, caused by the hepatitis A virus (HAV), is the most common type of viral hepatitis reported in the United States. Hepatitis A virus is extremely hardy; it can live for long periods of time outside of its host and cannot be destroyed by bleach or freezing temperatures. The virus is transmitted from person-to-person between household contacts or sex partners, or by contaminated food or water. In rare cases, Hepatitis A can be transmitted as a blood-borne pathogen, much like hepatitis B and C. This disease can cause jaundice, fatigue, abdominal pain, anorexia, fever and nausea. This disease can result in sudden, severe liver failure and claims over 100 lives each year. The vaccine is recommended for travelers to countries with high or intermediate rates of HAV infection, children two years of age and older in communities with consistently high rates of hepatitis A, men who have sex with men, illegal drug users, persons with chronic liver disease, persons with clotting-factor disorders and persons who work with HAV-infected primates or with HAV in a research laboratory setting.[1-3]

Benefit from Vaccination

Hepatitis A vaccine can provide long-term protection against HAV infection for persons two years of age and older. Approximately 10 cases of hepatitis A are reported per 100,000 population each year. However, hepatitis A occurs in epidemics both nationwide and in communities every five to 10 years when rates of disease have been as high as 700 cases per 100,000 persons. This disease leads to about 100 deaths in the United States per year. Patients with hepatitis A suffer substantial morbidity and require hospital care in 11% to 22% of cases. Children play an important role in transmission of this disease and serve as both a source and reservoir of infection for others. Because most children have unrecognized infections and some appear asymptomatic,[3] this disease is often underreported. In 2000, 13,397 cases of this disease were reported.[4] However, a recent scientific model has predicted that the actual incidence of hepatitis A is 7.4 to 13.9 times the number of cases that are reported.[5]

Hepatitis A vaccine is of particular importance in communities with high rates of hepatitis A disease. For example, vaccination offered to children ages two to 12 years from January 1995 through December 2000 in a California community with elevated rates of the disease reduced the number of hepatitis A cases reported in the entire county by 93.5%.[6] Communities with consistently high rates of hepatitis A disease typically have epidemics every 5-10 years, with each episode lasting several years. In the late 1990s, however, hepatitis A vaccine was more widely used, and the number of cases reached historic lows.[3]

Each month, about 20 out of 1,000 travelers to foreign countries become infected with HAV.[7] Only travelers to North America (except Mexico and Central America), western Europe, Japan, Australia and New Zealand are at no increased risk for hepatitis A.[3]

HAV infection causes great concern to food service establishments. Food handlers infected with HAV can potentially expose thousands of people. In such cases, one infected food handler can damage the name and reputation of the establishment, decrease sales, accrue significant medical costs, reduce productivity, consume corporate time and prompt litigation. Reported sales losses can be up to 80% and, in some instances, businesses have been forced to close.[8] During these outbreaks, the resources of the overtaxed public health departments charged with managing the predicament are considerably drained. Extra nursing staff is needed to handle the influx of patients, disease education and vaccination. Extra time, effort and more people are necessary to investigate the cause of the outbreak and identify all persons who may have been exposed.

Risk of Vaccine Adverse Events

About half of the adults and children who receive the hepatitis A vaccine will experience no adverse events.[2] Mild reactions such as injection site tenderness, pain or swelling has been reported in 20% to 50% of recipients. Less than 10% of vaccinees

GLOSSARY TERMS

Acute
Adverse events
Advisory Committee on Immunization Practices
Anorexia
Background incidence
Cases
Chronic
Coverage
Disease
Efficacy
Epidemic
Hepatitis
Hepatitis A
Immunization
Jaundice
Liver failure
Morbidity
Nausea
Risk
Systemic
Vaccine
Vaccine Adverse Events Reporting System
Virus

ACRONYMS

HAV	Hepatitis A virus
HAVRIX®	Hepatitis A vaccine (GlaxoSmithKline)
VAERS	Vaccine Adverse Events Reporting System
VAQTA®	Hepatitis A vaccine (Merck & Co.)

WEB RESOURCES

HEPATITIS A:

National Partnership for Immunization
http://www.partnersforimmunization.org/hepatitisa.html

Centers for Disease Control and Prevention's *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)*
http://www.cdc.gov/nip/publications/pink/hepa.pdf

National Center for Infectious Diseases
http://www.cdc.gov/ncidod/diseases/hepatitis/a/index.htm

Hepatitis Foundation International
http://www.hepfi.org

National Network for Immunization Information
http://www.immunizationinfo.org/database.index.cfm

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/each_vaccine2.shtml#name18

Immunization Action Coalition
http://www.immunize.org/hepA

HEPATITIS A VACCINE:

National Partnership for Immunization
http://www.partnersforimmunizationorg/hepatitisa.html

Centers for Disease Control and Prevention's *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)*
http://www.cdc.gov/nip/publications/pink/hepa.pdf

Recommendations of the Advisory Committee on Immunization Practices (ACIP)
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4812al.htm

Vaccine Information Statement
http://www.cdc.gov/nip/publications/vis/vis-hep-a.pdf

Immunization Action Coalition
http://www.immunize.org/catg.d/2081ab.htm

VACCINE MANUFACTURER:

GlaxoSmithKline
http://www.worldwidevaccines.com/public/diseas/hepatoc.asp

Merck Vaccine Division
http://www.merckshardpdohme.com/disease/preventable/hepa

report mild systemic complaints, fatigue and low grade fever.[1] No serious adverse reactions to this vaccine have been reported.[1,3]

Cost-Benefit Analysis

Adults who become ill with hepatitis A lose an average of 27 work-days per illness and health departments treat about 11 potentially exposed contacts per one infected person. The average direct and indirect costs of hepatitis A disease range from $1,817 to $2,459 per adult case and $433 to $1,492 per pediatric case.[8] In a 1996 hepatitis A outbreak in Colorado involving 43 persons, the estimated total cost was $800,000.[9] When 65% to 80% vaccination rates of preschool and school-age children are achieved and routine vaccination is sustained, ongoing outbreaks of hepatitis A are effectively interrupted, a sustained reduction in disease incidence has been observed and subsequent outbreaks prevented.[10-14]

Safety Studies

- A two-year safety review of the Vaccine Adverse Events Reporting System (VAERS) hepatitis A safety data revealed that following distribution of more than six million doses, 19 persons (approximately three events per one million doses used) reported unexpected vaccine-associated events.[15]
- A study involving the vaccination of 29,789 children ages two to 12 years reported no serious adverse events following vaccination. Reported adverse reactions were generally mild and included reactions at the site of injection, fever and rash.[6]
- The safety of hepatitis A vaccination was evaluated in 37 vaccinated liver transplant patients who were compared to 45 unvaccinated control patients. (Liver transplant patients frequently suffer from chronic liver disease related to tissue rejection, recurrence of pretransplantation disease or complications following transplantation that put them at increased risk for liver failure associated with acute hepatitis A infection.) Although hepatitis A vaccine efficacy was found to be low in these patients, immunization was found to be safe and well tolerated. Headache was the most frequent side effect reported by the patients involved in this study.[16]
- Protective efficacy studies of approximately 50,000 persons given the hepatitis A vaccine, HAVRIX®, did not attribute any reported adverse events to the vaccine.[17] Likewise, studies on the newer hepatitis A vaccine, VAQTA®, followed 9,200 persons and found no adverse events related to the vaccine.[18]
- An estimated 1.3 million persons had been vaccinated with HAVRIX® by 1999. The rates of serious adverse events for these persons for which background incidence data are known are not higher than would be expected for an unvaccinated population. An estimated 20,000 persons had been administered VAQTA® by 1999, and no adverse events had been reported.[3]

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HEPATITIS B VACCINE

General Disease Information

Hepatitis B is a liver disease caused by hepatitis B virus (HBV). HBV is transmitted from individuals with acute or chronic infection, through contact with their blood or bodily fluids containing blood. This can occur through direct blood-to-blood contact, unprotected sex, illicit drug use, unsterile needles or from an infected woman to her newborn during the delivery process. In certain circumstances hepatitis B can be considered a sexually transmitted disease.

Acute hepatitis B disease can cause liver failure and lead to death. Chronic hepatitis B disease can cause long-term liver damage, including cirrhosis and liver cancer. Groups at risk for HBV infection include: persons with multiple sex partners or who have a diagnosis of a sexually transmitted disease, men who have sex with men, sexual contacts of infected persons, injection drug users, household contacts of chronically infected persons, infants born to infected mothers, infants or children of immigrants from areas with high rates of HBV infection, health care and public safety workers, individuals living or working in institutional settings such as prisons and group homes, and hemodialysis patients.[1, 2]

Benefit from Vaccination

Hepatitis B vaccination is the best protection against acquiring HBV infection. The number of new infections per year has declined from an average of 450,000 in the 1980s when the hepatitis B vaccine was first introduced to about 180,000 in 1998. The greatest decline occurred among children and adolescents and is a result of routine hepatitis B vaccination.

However, one out of every 20 persons (or about 12.5 million persons) has been infected with hepatitis B during their lifetime, an estimated 1.25 million Americans have chronic, lifelong hepatitis B infection and 4,000-5,500 deaths occur each year in the US from hepatitis B-related chronic liver disease such as cirrhosis and liver cancer.[2] More widespread use of currently available vaccine could prevent up to one million deaths worldwide due to hepatitis B-associated liver cirrhosis and liver cancer.[4]

High vaccine coverage levels need to be maintained to prevent transmission of HBV from infected individuals to susceptible contacts. Approximately 10% of all acute HBV infections progress to chronic infection (the risk of chronic infection decreases as age increases). Of the chronic cases of hepatitis B, 20% to 30% acquired their infection in childhood. These persons are a reservoir for transmission to others.[5]

The risk of chronic hepatitis B infection decreases as age increases. As many as 90% of infants exposed to hepatitis B from their mothers at birth become carriers. Thirty to fifty percent of affected children between one and five years of age become carriers. But by adulthood, the risk of becoming a carrier is 6% to 10%.[1]

Risk of Vaccine Adverse Events

More than 65% of children who receive the hepatitis B vaccine will experience no adverse events. The adverse events that do occur are primarily mild reactions such as injection site tenderness or mild fever.[6] A rare side effect of hepatitis B vaccine is anaphylaxis, a type of allergic reaction. This reaction occurs in about one case per 600,000 doses given. Recent studies have shown no association between hepatitis B vaccination and multiple sclerosis.[7] (See *Vaccine Safety Issues* on page 97.) No deaths from hepatitis B vaccination have been reported.

Cost-Benefit Analysis

The cost of acute and chronic hepatitis B disease in the US is estimated at $658 million in 1992 dollars.[8] A cost analysis of hepatitis B vaccination was conducted in Iowa, a state where the annual attack rate is low—approximately one-sixth that of national levels. This study found that routine infant immunization would prevent 45.7 cases

GLOSSARY TERMS

Acute
Adverse events
Advisory Committee on Immunization Practices
Anaphylaxis
Association
Cases
Chronic
Cirrhosis
Coverage
Disease
Guillain-Barré syndrome
Hemodialysis
Hepatitis
Hepatitis B
Immunization
Liver failure
Placebo
Risk
Seizure
Vaccine
Virus

ACRONYMS

HBV	Hepatitis B Virus
VAERS	Vaccine Adverse Events Reporting System

WEB RESOURCES

HEPATITIS B:

National Partnership for Immunization
http://www.partnersforimmunization.org/hepatitisb.html

Centers for Disease Control and Prevention's *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)*
http://www.cdc.gov/nip/publications/pink/hepb.pdf

National Center for Infectious Diseases
http://www.cdc.gov/ncidod/diseases/hepatitis/b/index.htm

Hepatitis Foundation International
http://www.hepfi.org

National Network for Immunization Information
http://www.immunizationinfo.org/database/index.cfm

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/each_vaccine2.shtml#name10

Immunization Action Coalition
http://www.immunize.org/hepB

HEPATITIS B VACCINE:

National Partnership for Immunization
http://www.partnersforimmunization.org/hepatitisb.html

Recommendations of the Advisory Committee on Immunization Practices (ACIP)
http://www.cdc.gov/mmwr/preview/mmwrhtml/00056293.htm

Vaccine Information Statement
http://www.cdc.gov/nip/publications/vis/vis-hep-b.pdf

National Center for Infectious Diseases
http://www.cdc.gov/ncidod/diseases/hepatitis/b/index.htm

VACCINE MANUFACTURERS:

Merck Vaccine Division
http://www.merckshapdohme.com/disease/preventable/hepb

GlaxoSmithKline
http://www.worldwidevaccines.com/public/diseas/hepbtoc.asp

of infection per 10,000 newborns, and save a total of 52 years of life per year. A proposal to immunize all Iowans as teenagers (except individuals born to mothers known to be infected with HBV, who would continue to be immunized at birth), was found to be more costly and would prevent less disease than would be achieved by immunizing all newborns.[9]

Safety Studies

- Safety studies have shown that the most frequently reported adverse events of hepatitis B vaccination are pain at the site of injection (3% to 29%) and fever (1% to 6%),[10,11] but that these effects occurred no more frequently among people receiving the vaccine than among those receiving a placebo.[12,13]
- In Taiwan, Alaska and New Zealand, large-scale infant immunization programs have not detected an association between hepatitis B vaccination and the occurrence of severe adverse events, including seizures, Guillain-Barré syndrome or anaphylaxis.[14,15]
- A review of Vaccine Adverse Event Reporting System (VAERS) case reports from 1991-1994 concluded that no unexpected adverse events occurred after more than 12 million doses of vaccine were given to infants.[16]
- A Canadian study evaluating health problems occurring one month before and one month after vaccination with the hepatitis B vaccine in 1,130 children (all about nine years of age) found only a minimal increase in the incidence of adverse events after vaccination.[17]

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INACTIVATED POLIOVIRUS (IPV) VACCINE

General Disease Information

Polio is remembered by many people as a frightening viral disease that was epidemic during the 1950s. Poliomyelitis affects the lymphatic and nervous system and is spread by contact with an infected person or their stool. Polio symptoms begin with fever, sore throat, headache and stiff neck and can quickly progress to paralysis of the limbs and chest, making walking and breathing difficult to impossible. There is no cure for this disease.[1-3]

Benefit from Vaccination

Vaccination with inactivated poliovirus (IPV) vaccine prevents children from becoming infected with poliovirus. In 1952, more than 20,000 people—mostly children—were diagnosed with polio. Before the polio vaccine was introduced in the US, 13,000 to 20,000 people became paralyzed from this disease and 1,000 people died each year.[4] IPV vaccine was licensed in 1955 and was used extensively until the early 1960s. In 1963, oral poliovirus (OPV) vaccine was licensed and largely replaced IPV vaccine because this live-attenuated vaccine was more effective at producing community immunity. Nearly exclusive use of OPV led to elimination of wild-type poliovirus from the US in less than 20 years.[1] Today due to high population coverage rates and safety considerations (see Safety Studies below) we have returned to using IPV.

Risk-Benefit Analysis

The last case of natural or "wild-type" poliovirus infection in the United States was in 1979, and global polio eradication is currently underway. According to provisional data from the Centers for Disease Control and Prevention (CDC), the number of cases of paralytic polio in the US has been reduced from an average of 16,316 cases each year during the course of the twentieth century to zero cases in 2000.[5] Outbreaks of polio continue to occur in Africa and Asia. The virus could be imported to the US via international travelers if vaccine coverage levels are not maintained. Until polio is eradicated worldwide, people in the US remain at risk. The US can remain free of poliomyelitis by continuing to vaccinate children with IPV to reduce the risk that importation of poliovirus will result in outbreaks of polio.[1]

Risk of Vaccine Adverse Events

Most children experience no adverse events after IPV immunization. Some children experience mild reactions such as tenderness at the injection site. IPV vaccine has caused no serious adverse events.[6]

Cost-Benefit Analysis

The Poliomyelitis Eradication Initiative examined the net costs and benefits of polio vaccination during the period 1986-2040. The model assumed different vaccine delivery costs in industrialized and developing countries, and ignored all benefits aside from reductions in direct costs for treatment and rehabilitation. The model predicted that the benefits will exceed the costs during 2007, with a cumulative savings of $13,600 million by the year 2040.[7]

Safety Studies

- During the period of OPV use, approximately one case of vaccine-associated paralytic polio was observed for every 2.4 million doses administrated.[8] In order to reduce the occurrence of vaccine-associated paralytic polio, the Advisory Committee on Immunization Practices (ACIP) recommended an increase in the use of IPV vaccine through a sequential schedule of IPV vaccine followed by OPV vaccine. As of January 1, 2000, ACIP recommends that IPV vaccine be used exclusively in

GLOSSARY TERMS

Adverse events
Advisory Committee on Immunization Practices
Cases
Community immunity
Coverage
Disease
Epidemic
Immunization
Inactivated poliovirus vaccine
Lymphatic system
Nervous system
Oral poliovirus vaccine
Poliomyelitis Eradication Initiative
Risk
Vaccine
Virus
Wild-type

ACRONYMS

ACIP	Advisory Committee on Immunization Practices
CDC	Centers for Disease Control and Prevention
IOM	Institute of Medicine
IPV	Inactivated poliovirus
OPV	Oral poliovirus

WEB RESOURCES

POLIO:

National Partnership for Immunization
http://www.partnersforimmunization.org/polio.html

Centers for Disease Control and Prevention's *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)*
http://www.cdc.gov/nip/publications/pink/polio.pdf

National Network for Immunization Information
http://www.immunizationinfo.org/database/index.cfm

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/each_vaccine2.shtml#name04

Immunization Action Coalition
http://www.immunize.org/polio

INACTIVATED POLIO VACCINE:

National Partnership for Immunization
http://www.partnersforimmunization.org/polio.html

Recommendations of the Advisory Committee on Immunization Practices (ACIP)
ftp://ftp.cdc.gov/pub/Publications/mmwr/rr/rr4905.pdf

Recommendations of the American Academy of Pediatrics (AAP)
http://www.aap.org/policy/re9949.html

Vaccine Information Statement
http://www.cdc.gov/nip/publications/vis/vis-ipv.pdf

VACCINE MANUFACTURER:

Aventis Pasteur
http://www.us.aventispasteur.com/vaccines/polio/main.htm

the US. Unlike OPV, IPV cannot replicate in the intestine of a vaccinated person. Therefore, IPV cannot be shed by a vaccinated person into the environment and possibly infect others with poliovirus.[1]

- Beginning in 1954, a total of 1,829,916 children from all parts of the US took part in the largest experiment of its kind up to that time to test the IPV vaccine. The vaccine was found to be safe and effective and was licensed within a few days after the announcement of the results of the field trial.[9]
- According to CDC, no serious adverse events related to IPV have been documented since IPV vaccine use was expanded in 1996.[10]
- An Institute of Medicine (IOM) Safety Committee found no serious adverse events associated with the use of IPV vaccine in countries relying on all-IPV childhood immunization schedules.[11]

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INFLUENZA VACCINE

General Disease Information

Influenza (flu) is a highly contagious viral infection which affects the nose, throat and lungs. Influenza is spread easily from person to person via droplets, primarily when an infected person coughs or sneezes. It may lead to hospitalization or even death, especially among the elderly. In 1918-1919, the "Spanish flu" pandemic caused an estimated 21 million deaths worldwide.[1]

Benefit from Vaccination

Influenza vaccine prevents up to 40% of people who are exposed to the highly contagious disease of influenza from becoming ill.[2] In the average year, influenza is associated with over 20,000 deaths and 114,000 hospitalizations nationwide.[3] During most influenza seasons, approximately 10% to 20% of the population is infected with the influenza virus, although rates of infection vary among different age groups and from one season to another.[1]

The primary objective of preventing influenza is to reduce the incidence of severe illness and premature death in groups at increased risk of severe disease and, as a consequence, reduce the need for specialized health care services and pharmaceutical supplies, in particular antiviral drugs and antibiotics.[4] Influenza can lead to bacterial pneumonia, viral pneumonia or exacerbation of underlying medical conditions, e.g., chronic obstructive pulmonary disease, congestive heart failure.[1] Serious complications of influenza resulting in hospitalization or death most often occur in persons over 65 years of age, high-risk children or children younger than four years.[5]

The burden of influenza illness is greatest among children with asthma and other chronic medical conditions. During months when the influenza virus is circulating, this group experiences high rates of hospitalization and outpatient morbidity.[6-9] Among elderly persons, the vaccine is 50% to 60% effective in preventing hospitalization and 80% effective in preventing death.[10] A recent study assessed the outcomes of 259,627 persons age 65 years or older who were offered influenza and pneumococcal vaccines. Researchers found that the incidence of hospital treatment for influenza, pneumonia, pneumococcal pneumonia and invasive pneumococcal disease was significantly lower in the vaccinated group as compared to the unvaccinated group and that total mortality was 57% lower among vaccinated individuals.[11] The influenza vaccine is up to 90% effective in preventing illness among persons less than 65 years of age when the type of vaccine used is similar to the circulating influenza virus.[12]

Influenza vaccination of Japanese children from 1962 to 1987 prevented about 37,000 to 49,000 deaths in Japanese persons across all age groups per year, or about one death for every 420 children vaccinated. As the vaccination of schoolchildren was discontinued, the flu-related mortality rates of the general population in Japan increased.[13]

Risk of Vaccine Adverse Events

About 80% of people who receive the influenza vaccine will experience no adverse events.[7] Fifteen to twenty percent of vaccines will have minor adverse events such as tenderness or redness at the injection site.[3] Fever, muscle aches or malaise lasting one to two days occurs in less than 1% of people who receive the influenza vaccine. In rare instances, an immediate allergic reaction, which can include hives, asthma, swelling of the throat, low blood pressure or shock occurs. Persons allergic to egg proteins are at an increased risk for such an allergic reaction and should follow published protocols regarding influenza vaccination.[2, 14]

Cost-Benefit Analysis

The 1918-1919 influenza pandemic is believed to have resulted in the death of 550,000 Americans and 21 million people worldwide.[2] Analysts forecast that today a

GLOSSARY TERMS

Acute
Adverse events
Advisory Committee on Immunization Practices
Antibiotic
Asthma
Background incidence
Chronic
Chronic obstructive pulmonary disease
Congestive heart failure
Disease
Epidemic
Guillain-Barré syndrome
Heart failure
Immunization
Influenza
Invasive
Morbidity
Pandemic
Placebo
Pneumococcal disease
Pneumonia
Protein
Risk
Spanish flu
Systemic
Vaccine
Virus

WEB RESOURCES

INFLUENZA:

National Partnership for Immunization
http://www.partnersforimmunization.org/influenza.html

Centers for Disease Control and Prevention
http://www.cdc.gov/ncidod/diseases/flu/fluvirus.htm

National Foundation for Infectious Diseases
http://www.nfid.org/library/influenza

Centers for Disease Control and Prevention's *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)*
http://www.cdc.gov/nip/publications/pink/flu.pdf

National Network for Immunization Information
http://www.immunizationinfo.org/database/index.cfm

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/each_vaccine2.shtml#name13

Immunization Action Coalition
http://www.immunize.org/influenza

INFLUENZA VACCINE:

National Partnership for Immunization
http://www.partnersforimmunization.org/influenza.html

Recommendations of the Advisory Committee on Immunization Practices (ACIP)
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4903al.htm

Vaccine Information Statement
http://www.cdc.gov/nip/publications/vis/vis-flu.pdf

VACCINE MANUFACTURERS:

Aventis Pasteur
http://www.us.aventispasteur.com/vaccines/flu/main.htm

Wyeth Vaccines
http://www.wyeth.com/products/flushield.asp

similar influenza pandemic could lead to up to 207,000 deaths in the US.[15] During a regular flu season in the US, influenza accounts for $1-3 billion in direct medical costs; indirect costs, including lost earnings due to illness and lost future earnings due to death, are in the range of $10-15 billion a year.[16]

Along with pneumococcal vaccine, the influenza vaccine appears to be more cost-effective than any other medical intervention commonly used in the care of the elderly (this includes mammograms, bypass surgery and hypertension screening).[17] A study of six cohorts, each including more than 20,000 persons over 64 years of age, reported a direct medical care cost savings per year averaging $73 per person vaccinated. Vaccination was also associated with a 50% reduction in mortality from pneumonia, influenza, all acute and chronic respiratory conditions and congestive heart failure during the three influenza seasons studied.[18]

Influenza vaccination of healthy working adults aged 18 to 64 years has also been found to be cost saving. Taking into account both direct and indirect cost savings resulting from vaccination, this population saved an average of $13.66 per person vaccinated.[19]

Safety Studies

- Reports have described exacerbations of asthma following influenza vaccination. However, the vaccine is administered at the time of year when the background incidence of asthma activity is high. A causal relationship between influenza vaccine and the development of asthma has not been established[20] and results from a recent study show that influenza vaccination does not result in exacerbation of asthma in children.[21]
- A study of two influenza seasons has shown that the increased risk of developing Guillain-Barré syndrome in the vaccinated population is approximately one case per one million influenza vaccinations.[22] Guillain-Barré syndrome is a rare neurological disease that is characterized by loss of reflexes and temporary paralysis. Even if Guillain-Barré syndrome was a side effect of influenza vaccination, the estimated risk for this disease would be substantially less than the risk of developing severe influenza in the absence of vaccination.[23]
- A study evaluating the usefulness of administering influenza immunization to hospitalized patients noted that 74% of reported side effects were reported to be not significant. The most common side effect reported was soreness at the site of vaccine injection (12%).[24]
- A trial was performed in the UK using 729 healthy individuals with a median age of 68.9 years who received either the influenza vaccine or a placebo. No significant difference in reported systemic symptoms (fever, aching limbs, fatigue, rash, cough, runny nose, headache and sore throat) between vaccine and placebo groups was found. Only local side effects occurred with a significantly increased incidence following influenza vaccination in healthy older people when compared to placebo. No individual had to seek medical advice because of side effects and participants did not inform researchers of any severe reactions following vaccination.[25]

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MEASLES, MUMPS, RUBELLA (MMR) VACCINE

General Disease Information

Measles is a highly contagious respiratory disease caused by a virus. Symptoms of measles last for about a week and include rash, high fever, cough, runny nose and red, watery eyes. More severe complications include pneumonia, encephalitis, seizures and death. The most common causes of measles-associated death are pneumonia in children and acute encephalitis in adults. During pregnancy, measles illness results in an increased risk of premature labor, spontaneous abortion and low birthweight infants. Measles in immunosuppressed persons may be severe and prolonged.[1-3]

Mumps is a viral disease that usually begins with swollen salivary glands. Serious complications of mumps include swelling of the testicles in adolescents and adults, deafness, aseptic meningitis and death. Women who develop mumps during the first trimester of pregnancy have an increased risk for fetal death.[3-6]

Rubella, also called German measles, is often a mild rash illness when contracted by adult males and children. However, arthritis or arthralgia has been reported in up to 70% of women who contract this disease but is rare in children and adult males.[7] Infection of a pregnant woman can cause devastating birth defects to the developing child and could be followed by a disease called congenital rubella syndrome (CRS), which may lead to fetal death or premature delivery, deafness, cataracts, heart defects, abnormalities of the nervous system, mental retardation, bone alterations, and liver and spleen damage. Fifty percent of infected people will have no disease symptoms.[3, 5]

Benefits from Vaccination

Measles, mumps and rubella (MMR) vaccination prevents the diseases of measles, mumps and rubella. Before MMR vaccine was introduced, approximately 500,000 cases of measles[8] and 500 measles-associated deaths were reported annually with epidemics occurring every 2-3 years.[9] Following licensure of a vaccine in 1963, the incidence of measles decreased by more than 98% and epidemic cycles no longer occurred. The Centers for Disease Control and Prevention (CDC) reports that the number of measles cases has been reduced from an average of 503,282 cases per year during the pre-vaccine era to 86 cases in 2000.[8]

Measles virus outbreaks still occur in the US. Therefore, decreased use of the measles vaccine would likely result in the resurgence of measles.[10] Discontinuing measles vaccination in the US and the eventual loss of community immunity would result in an eventual return to pre-vaccine era rates of disease that include three million to four million cases of measles each year and more than 1,800 deaths, 1,000 cases of encephalitis and 80,000 cases of pneumonia.[11]

The impact of decreased immunization coverage was demonstrated between 1989 and 1991 when low vaccination rates caused a rise in the number of measles cases.[5] During these three years, a total of 55,467 measles cases and 136 measles-associated deaths were reported.[12] Reported cases of measles declined rapidly thereafter due primarily to intensive efforts to vaccinate preschool-aged children.[5]

Mumps and rubella outbreaks have also occurred but the number of reported cases of these diseases has significantly declined since MMR vaccine was introduced.[13] The US is on the verge of eliminating rubella, but the 31 outbreaks of rubella that have been reported in the US since 1993 serve as a reminder that this disease continues to occur. In 1964, a rubella outbreak in the US resulted in 12.5 million cases of rubella infection and 20,000 newborns with CRS.[5] The most prominent outbreak setting has been worksites, followed by communities and correctional facilities.[14] Like measles, mumps has been reduced from 152,209 cases in the pre-vaccine era to 338 cases in 2000.[7] Similarly, the number of cases of rubella fell from 47,745 cases to 176 cases in 2000.[7]

GLOSSARY TERMS

Acute
Adverse events
Advisory Committee on Immunization Practices
Arthralgia
Arthritis
Aseptic meningitis
Association
Autism
Cases
Cataracts
Chronic
Coma
Community immunity
Congenital rubella syndrome
Coverage
Crohn's disease
Disease
Efficacy
Encephalitis
Encephalopathy
Epidemic
German measles
Guillain-Barré syndrome
Immunization
Measles
MMR vaccine
Mumps
Placebo
Pneumonia
Risk
Rubella
Salivary glands
Seizure
Testicles
Vaccine
Vaccine Safety Datalink Project
Virus

ACRONYMS

CDC	Centers for Disease Control and Prevention
CRS	Congenital rubella syndrome
MMR	Measles, mumps, rubella
PAHO	Pan American Health Organization

WEB RESOURCES

MEASLES:

National Partnership for Immunization
http://www.partnersforimmunization.org/mmr.html

Centers for Disease Control and Prevention's *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)*
http://www.cdc.gov/nip/publications/pink/meas.pdf

National Network for Immunization Information
http://www.immunizationinfo.org/database/index.cfm

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/each_vaccine2.shtml#name07

Immunization Action Coalition
http://www.immunize.org/measles

MUMPS:

National Partnership for Immunization
http://www.partnersforimmunization.org/mmr.html

Centers for Disease Control and Prevention's *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)*
http://www.cdc.gov/nip/publications/pink/mumps.pdf

National Network for Immunization Information
http://www.immunizationinfo.org/database/index.cfm

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/each_vaccine2.shtml#name08

Immunization Action Coalition
http://www.immunize.org/mumps

RUBELLA: (continued)

Risk of Vaccine Adverse Events

More than 80% of children who receive this vaccine will experience no adverse events. The majority of adverse events that do occur will be mild and include tenderness, redness or swelling at the injection site, rash, fever, swelling of the lymph glands and temporary joint pain, stiffness or swelling. In about three cases out of 10,000 injections given, high fever will result in a seizure. In very rare cases of one case out of 100,000 injections, MMR vaccine may cause a temporary bleeding problem or seizures related to high fever, lowered consciousness or coma.[6]

Cost-Benefit Analysis

A childhood measles, mumps and rubella immunization program using MMR vaccine in the United States was found to have prevented 3,322,128 cases of measles, 2,067,150 cases of mumps and 1,496,184 cases of rubella. The cost-benefit ratio calculated from this study found that for every $1 spent on the MMR immunization program $14 were saved.[15] According to the CDC, the estimated cost of the 1964 rubella epidemic that resulted in 20,000 cases of CRS was $840 million. Today, the lifetime cost of one case of CRS is estimated to be in excess of $200,000.[7]

Safety Studies

- It has been postulated that use of the MMR vaccine may be associated with the development of inflammatory bowel disease and/or autism.[16] The available scientific evidence does not support this hypothesis, but these issues are discussed in greater detail in the section *Vaccine Safety Issues*.
- 1.8 million Finnish children immunized with nine million doses of MMR vaccine were followed by researchers from the time MMR vaccine was first introduced in Finland in 1982 until 1996. No cases of autism or Crohn's disease were reported. A safety analysis determined that serious events related to MMR vaccine were rare and were greatly outweighed by the risks of the diseases the vaccine prevents.[17]
- A study was conducted on 1,162 identical and fraternal twins at 14 to 83 months of age, each receiving a placebo and then the vaccine, or vice versa, three weeks apart. The study population was followed for three weeks after each injection. No difference was found in reported minor reactions between vaccine and placebo recipients.[18]
- A study of the relationship between vaccination with a measles-containing vaccine and the development of acute encephalopathy in persons who were previously healthy found no increase in the risk of this disease or other nervous system problems after measles vaccination. [19]
- A study assessing the risk of hospitalization for aseptic meningitis within 30 days of MMR vaccination followed 300,000 vaccine doses and did not identify a single case of encephalopathy or encephalitis.[18]
- Analysis of 2,296 reported cases of Guillain-Barré syndrome identified no difference in the number of cases following measles vaccination compared with the number of expected cases during that time period.[19]
- Although a 1991 review by the Institute of Medicine found a possible association between rubella vaccination and chronic arthritis among women,[20] a later retrospective cohort study utilizing the Vaccine Safety Datalink Project reviewed the records of 4,884 women and found no evidence of an increased risk of the onset of chronic arthralgia, arthritis or neurologic conditions in women who were vaccinated against rubella.[21]
- A recent review of MMR vaccine safety data suggested that MMR vaccine pre-licensure safety studies were inadequate because only a few pre-licensure studies were conducted and because these studies had very short periods of follow-up observation of study participants.[22] The United Kingdom's Medicines Control Agency and Department of Health responded to this study by reassuring the

National Partnership for Immunization
http://www.partnersforimmunization.org/mmr.html

Centers for Disease Control and Prevention's *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)*
http://www.cdc.gov/nip/publications/pink/rubella.pdf

National Network for Immunization Information
http://www.immunizationinfo.org/database/index.cfm

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/each_vaccine2.shtml#name09

Immunization Action Coalition
http://www.immunize.org/rubella

MMR VACCINE:
National Partnership for Immunization
http://www.partnersforimmunization.org/mmr.html

Recommendations of the Advisory Committee on Immunization Practices (ACIP)
http://www.cdc.gov/mmwr/preview/mmwrhtml/00053391.htm

Vaccine Information Statement
http://www.cdc.gov/nip/publications/vis/vis-mmr.pdf

VACCINE MANUFACTURER:
Merck Vaccine Division
http://www.mercksharpdohme.com/disease/preventable/mmr

public that the licensing process for MMR was adequate to establish the safety, quality and efficacy of the vaccines. They noted that 30 research studies have been published that examined combined measles, mumps and rubella vaccines with follow ups of study participants extending up to 10 years.[23]

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MENINGOCOCCAL VACCINE

General Disease Information

Neisseria meningitidis bacteria are a leading cause of bacterial meningitis and sepsis in older children and young adults in the US. During 1991-1998, the highest rate of meningococcal disease occurred among infants under one year of age; however, the rate among persons ages 18-23 years was also higher than that for the general population. Certain medical conditions, household crowding, chronic illness and smoking increase the risk for developing meningococcal disease.[1]

Benefits from Vaccination

Meningococcal vaccine helps prevent meningococcal disease in persons age two years and older. This highly contagious disease can cause epidemics in child care centers, schools and universities.[2] Meningococcal vaccine protects against disease caused by four serotypes of *Neisseria meningitidis* bacteria; A, C, Y and W-135. Most outbreaks of meningococcal disease are caused by serotype C.[1]

Each year in the US, 2,400-3,000 cases of meningococcal disease occur at a rate of 0.8-1.3 cases per 100,000 population.[3-5] Although many antibiotics are very effective against *Neisseria meningitidis*,[6] 10% of people who contract meningococcal disease will die.[4] From January 1990 through December 1999, 25% of meningococcal infection cases among persons ages 15 through 24 years in Maryland were fatal.[7] Eleven to nineteen percent of persons who survive this disease will suffer from permanent neurologic disability, limb loss and hearing loss.[8,9]

In the US, African Americans, persons of low socioeconomic status, military recruits living in barracks and college students living in dormitories are at increased risk for meningococcal disease. A US Army field study found an 89.5% reduction in the rate of meningococcal disease in serotype C-vaccinated recruits compared to unvaccinated recruits.[10,11] As a result of this report, in October 1971, the US Army began requiring that all new recruits be vaccinated with this vaccine.[1,12] A recent study of college students found that the overall incidence rate for undergraduates was 0.7 per 100,000 compared to an incidence of meningitis of 1.4 per 100,000 for the general population of 18- to 23-year-old non-students. However, freshmen living in dormitories had the highest incidence rate at 5.1 per 100,000. Of the 79 cases for whom information was available, 54 (68%) had illness due to vaccine-preventable meningococcal serotypes.[13]

Risk of Vaccine Adverse Events

More than 50% of those receiving the meningococcal vaccine will have no adverse events. Up to 40% of people will experience mild reactions such as pain and redness at the injection site. Fever, the most common adverse reaction reported to the Vaccine Adverse Event Reporting System (VAERS),[14] may last one to two days. Approximately three people per 1,000,000 doses given can experience a serious allergic reaction resulting in breathing difficulties.[15] From July 1990 through October 1999, during which more than six million doses of meningococcal vaccine were distributed, 110 adverse events were reported to VAERS. The most common events reported were fever, headache and dizziness.[14]

Cost-Benefit Analysis

A cost-benefit analysis projected that a program to vaccinate all college freshmen living in dormitories would require the administration of 300,000-500,000 doses of vaccine per year. This program would prevent 15 to 30 cases of meningococcal disease and one to three deaths. The cost of the program per case prevented was found to be between $600,000 and $1.8 million and the cost per death prevented varied between $7 million and $20 million.[1]

GLOSSARY TERMS

Adverse events
Advisory Committee on Immunization Practices
Antibiotic
Association
Bacteria
Bacterial meningitis
Cases
Chronic
Clinical trials
Disease
Epidemic
Meningitis
Meningococcal disease
Neisseria meningitidis
Polysaccharide
Risk
Sepsis
Serotype
Vaccine

ACRONYMS

VAERS Vaccine Adverse Event Reporting System

WEB RESOURCES

MENINGOCOCCAL DISEASE:

National Partnership for Immunization
http://www.partnersforimmunization.org/mening.html

Center for Disease Control and Prevention's Division of Bacterial and Mycotic Diseases
http://www.cdc.gov/ncidod/dbmd/diseaseinfo/meningococcal_g.htm

National Foundation for Infectious Diseases
http://www.nfid.org/library/meningococcal

American College Health Association
http://www.acha.org/special-prj/mem.htm

National Network for Immunization Information
http://www.immunizationinfo.org/database/index.cfm

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/each_vaccine2.shtml#name15

Immunization Action Coalition
http://www.immunize.org/mening

MENINGOCOCCAL VACCINE:

National Partnership for Immunization Information
http://www.partnersforimmunization.org/mening.html

Recommendations of the Advisory Committee on Immunization Practices (ACIP)
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4907al.htm

Recommendations of the American Academy of Pediatrics (AAP)
http://www.aap.org/policy/re0035.html

Vaccine Information Statement
http://www.cdc.gov/nip/publications/vis/vis-mening.pdf

VACCINE MANUFACTURER:

Aventis Pasteur
http://www.us.aventispasteur.com/vaccines/meningitis/main.htm

Safety Studies

- Clinical trials of the group C vaccine in over 28,000 infants, children and young adults in the US, United Kingdom, Canada and Holland found that the vaccine was well-tolerated and caused no serious adverse events.[16]
- Between 1991 and 1998, a total of 4,568,572 doses of meningococcal vaccine were distributed in the US and 222 adverse events reported for a rate of 49 adverse events per one million doses given; no deaths were reported.[1]

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PNEUMOCOCCAL CONJUGATE VACCINE

General Disease Information

Worldwide, *Streptococcus pneumoniae* bacteria are a leading cause of serious illness among young children and are the most frequent cause of bacteremia, meningitis, pneumonia, sinusitis and severe ear infections. The highest rates of these diseases occur among young children, especially those under two years of age.[1] Higher rates of disease occur among African Americans, Alaskan Natives and specific Native American populations, compared with whites.[2] The highest rates of invasive disease occur among Navajo and Apache American Indian children with incidence rates of 557 to 2,396 cases per 100,000 children between the ages of one and two.[3]

Benefits from Vaccination

Pneumococcal conjugate vaccine protects children under five years of age from developing pneumonia, meningitis, sepsis, ear infections and sinusitis from pneumococcal disease. Annually, pneumococcal disease causes approximately 17,000 cases of invasive disease among children under age five years, resulting in 700 cases of meningitis and 200 deaths. Treatment of pneumococcal disease among young children is complicated by the emergence of disease strains that are resistant to penicillin and other antibiotics. Although a 23-valent polysaccharide vaccine is available to prevent pneumococcal disease, this vaccine is not effective in children under two years of age. A new vaccine was developed and licensed in 2000 that is able to prevent pneumococcal disease in children two years old and younger. This new conjugate vaccine contains polysaccharides from the seven most common serotypes of *Streptococcus pneumoniae* that cause 80% of pneumococcal infections in children less than six years old.[2]

Each year in the US, routine pneumococcal conjugate vaccination is estimated to prevent approximately 12,000 cases of pneumococcal meningitis and bacteremia, 53,000 cases of pneumococcal pneumonia, more than one million episodes of clinically diagnosed ear infections and 116 deaths due to pneumococcal infection.[4] Approximately 15 million hospital/doctor's office visits for ear infections and more than 500,000 ear tube placements occur in children each year in the US. Widespread use of pneumococcal conjugate vaccine could greatly decrease visits for ear infections.[5] A study of 1,662 infants enrolled in a randomized, double-blind efficacy trial found that the pneumococcal conjugate vaccine reduced the number of episodes of acute ear infection from any cause by 6%, culture-confirmed pneumococcal episodes by 34%, and the number of episodes due to the serotypes contained in the vaccine by 57%.[6]

Because of the prevalence of pneumococcal disease in the US, antibiotic therapy is commonly prescribed to resolve cases of pneumonia and ear infection.[4] Since antibiotic therapy was first introduced, disease-causing strains of *Streptococcus* have gradually acquired resistance to the antibacterial effects of many of the commonly used antibiotics.[4] Up to one-third of all pneumococcal bacteria isolated in patients in the US now demonstrate moderate to high-level resistance to penicillin and multiple antibiotics.[7-12] This resistance limits the therapeutic value of these medications, resulting in the potential for more serious and/or more persistent disease.[4] The acquisition of resistance has been attributed to the widespread use and misuse of antibiotics in clinical practice as well as to non-clinical uses of these agents.[13] As disease causing organisms acquire resistance to various medications, newer, more powerful broad-spectrum antibiotics must be used to treat infected patients. Already, evidence is accruing that *Streptococcus* is acquiring resistance to state-of-the-art antibiotics.[14] The potential loss of sensitivity to these drugs has profound implications for public health. Because pneumococcal diseases can be prevented through the use of the conjugate vaccine, increased usage of the vaccine could reduce disease prevalence.[4] This would reduce the use of antibiotics and thus impede the development of antibiotic resistance by these deadly pathogens.[5]

GLOSSARY TERMS

Acute
Acute otitis media
Adverse events
Advisory Committee on Immunization Practices
Antibiotic
Bacteremia
Bacteria
Cases
Conjugate vaccine
Disease
Efficacy
Immunization
Invasive
Meningitis
Pathogens
Penicillin
Pneumococcal disease
Pneumonia
Polysaccharide
Polysaccharide vaccine
Prevalence
Risk
Sepsis
Serotype
Sinusitis
Streptococcus pneumoniae
Sudden Infant Death Syndrome
Systemic
Vaccine
Valent

ACRONYMS

SIDS Sudden Infant Death Syndrome

WEB RESOURCES

PNEUMOCOCCAL DISEASE:

National Partnership for Immunization
http://www.partnersforimmunization.org/pneumo.html

National Foundation for Infectious Diseases
http://www.nfid.org/library/pneumococcal

Centers for Disease Control and Prevention's *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)*
http://www.cdc.gov/nip/publications/pink/pneumo.pdf

National Network for Immunization Information
http://www.immunizationinfo.org/database/index.cfm

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/each_vaccine2.shtml#name06

Immunization Action Coalition
http://www.immunize.org/pneumoconj

PNEUMOCOCCAL CONJUGATE VACCINE:

National Partnership for Immunization
http://www.partnersforimmunization.org/pneumo.html

Recommendations of the Advisory Committee on Immunization Practices (ACIP)
http://www.cdc.gov/mmwr/pdf/rr/rr4909.pdf

Vaccine Information Statement
http://www.cdc.gov/nip/publications/vis/vis-PneumoConjugate.pdf

VACCINE MANUFACTURER:

Wyeth Vaccines
http://www.prevnar.com

Risk of Adverse Events

Mild reactions such as injection site redness, tenderness or swelling will occur in 10% to 20% of children vaccinated with pneumococcal conjugate vaccine.[16] Moderate reactions, including fever, irritability and drowsiness occur in up to 40% of children vaccinated. No serious adverse events have been reported in large, pre-licensure studies.[7]

Cost-Benefit Analysis

A recent publication estimated that infant immunization would cost society $80,000 per year of life saved, $160 per case of ear infection prevented, $3,200 per case of pneumonia prevented, $15,000 per case of bacteremia prevented and $280,000 per episode of meningitis prevented.[17]

Safety Studies

- A large efficacy study in 23 medical centers within the Kaiser Permanente Medical Care Program of Northern California compared vaccinated and unvaccinated children in a total study population of 37,868 children. The study did not reveal any severe adverse events related to vaccination resulting in hospitalization or emergency room or clinic visits. Local and systemic reactions observed generally were mild and more severe local and systemic reactions were uncommon. The rate of sudden infant death syndrome (SIDS) observed in the study population was less than the rate observed in the state of California during 1996 and 1997, prior to use of this vaccine.[5]

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PNEUMOCOCCAL POLYSACCHARIDE VACCINE

General Disease Information

Streptococcus pneumoniae bacteria can cause bacteremia, pneumonia, sinusitis and meningitis. Pneumococcal disease is most common in children less than two years of age and adults over 40 years of age, and occurs more often in males than in females at all ages. Higher rates of disease occur among African Americans, Alaska Natives and specific Native American populations, compared with whites. Mortality rates are greatest among persons 65 years of age and older; mortality is also associated with higher frequency of complications of respiratory infections.[1]

Benefit from Vaccination

Pneumococcal polysaccharide vaccine protects persons older than two years of age from pneumonia, bacteremia and meningitis. Each year, pneumococcal disease causes approximately 175,000 hospitalized cases of pneumonia, more than 50,000 cases of bacteremia and 3,000 to 6,000 cases of meningitis. Five to seven percent of cases of pneumonia, about 20% of bacteremia cases and about 30% of meningitis cases will die from the disease. The death rate among persons suffering from these diseases increases significantly in elderly populations.[4] A recent study assessed the outcomes of 259,627 persons age 65 years or older who were offered influenza and pneumococcal vaccines. The incidence of hospital treatment for influenza, pneumonia, pneumococcal pneumonia and invasive pneumococcal disease was significantly lower in the vaccinated group as compared to the unvaccinated group, and total mortality was 57% lower in vaccinated individuals.[2] Efficacy estimations of the pneumococcal polysaccharide vaccine range from 56% to 81%, and immunity has been shown to last for at least six years.[3, 4]

Risk of Adverse Events

About half of the people who receive this vaccine will have no adverse events. Thirty to fifty percent will experience mild reactions such as injection site tenderness or redness usually lasting less than 48 hours and less than 1% will experience fever, chills or malaise. Very rare cases (less than one person per 10,000) will experience a serious reaction such as breathing difficulties, hives, paleness, weakness, increased heart rate or dizziness.[5]

Cost-Benefit Analysis

Along with the influenza vaccine, pneumococcal vaccine appears to be more cost-effective than any other medical intervention commonly used in the care of the elderly (this includes mammograms, bypass surgery and hypertension screening).[6] One study of persons aged 65 years and older in three geographic areas (Atlanta, GA; Franklin County, OH; and Monroe County, NY) estimated that 23 million elderly people unvaccinated in 1993 would have gained about 78,000 years of healthy life and saved $194 million if they had been vaccinated with pneumococcal polysaccharide vaccine. The results also suggested that pneumococcal vaccination is likely to be even more cost saving for African Americans than for the general population. African Americans have rates of pneumococcal bacteremia more than twice those of whites, but vaccination rates are only about half as high.[7]

An observational study assessing the effectiveness of implementing an emergency department-based pneumococcal vaccination program found that doing so would result in overall cost savings ranging from $168,940 to $427,380 per year.[8]

Safety Studies

- Severe systemic adverse effects have rarely been reported after administration of pneumococcal polysaccharide vaccine, and no neurologic disorders have been associated with the vaccine.[1]

GLOSSARY TERMS

Adverse events
Advisory Committee on Immunization Practices
Anaphylaxis
Bacteremia
Bacteria
Cases
Disease
Efficacy
Immunization
Immunocompetent
Immunosuppressed
Invasive
Neurologic disorder
Pneumococcal disease
Pneumococcal polysaccharide
Pneumonia
Polysaccharide
Polysaccharide vaccine
Risk
Sinusitis
Streptococcus pneumoniae
Systemic
Vaccine

WEB RESOURCES

PNEUMOCOCCAL DISEASE:

National Partnership for Immunization
http://www.partnersforimmunization.org/pneumo.html

National Foundation for Infectious Diseases
http://www.nfid.org/library/pneumococcal

Centers for Disease Control and Prevention's *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)*
http://www.cdc.gov/nip/publications/pink/pneumo.pdf

National Network for Immunization Information
http://www.immunizationinfo.org/database/index.cfm

Immunization Action Coalition
http://www.immunize.org/pneumopoly

PNEUMOCOCCAL POLYSACCHARIDE VACCINE:

National Partnership for Immunization
http://www.partnersforimmunization.org/pneumo.html

Recommendations of the Advisory Committee of Immunization Practices (ACIP)
http://www.cdc.gov/mmwr/pdf/rr/rr4608.pdf

Vaccine Information Statement
http://www.cdc.gov/nip/publications/vis/vis-ppv.pdf

VACCINE MANUFACTURERS:

Merck Vaccine Division
http://www.merckshardpdohme.com/disease/preventable/pneu

Wyeth Vaccines
http://www.vaccineworld.com

- Analysis of nine randomized controlled trials of pneumococcal vaccine efficacy found that local, minor reactions were observed in one-third or fewer of 7,531 patients receiving the vaccine. No reports of severe fever or anaphylaxis were reported.[9]
- Revaccination with pneumococcal polysaccharide vaccine has not been associated with severe adverse reactions. Mild localized reactions have been associated with higher levels of circulating anti-pneumococcal antibodies. Therefore, a larger proportion of immunocompetent persons have reported local reactions such as redness, stiffness and pain at the injection site, than immunosuppressed persons. Mild to moderate fever was the most common systemic reaction reported by re-vaccinees and first-time vaccinees. Elevated temperatures did not last more than two days.[10]

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VARICELLA VACCINE

General Disease Information

Varicella, or chickenpox, is a highly contagious disease caused by varicella zoster virus that is transmitted by airborne droplets and direct contact with lesions. In the pre-vaccine era, the majority of cases of chickenpox (more than 90%) occurred among children under 15 years of age. Varicella complications include bacterial infection of skin lesions and dehydration; more serious complications that may result in hospitalization and death[1,2] include invasive group A streptococcus infections, hemorrhagic complications, encephalitis and pneumonia. Herpes zoster or shingles is caused by reactivation of the chickenpox virus and develops most frequently among immunocompromised persons and the elderly. In children, chickenpox generally lasts four to five days and usually involves between 250 to 500 lesions.[1]

Benefits from Vaccination

Before the varicella vaccine became available, approximately four million cases occurred annually in the US, resulting in 11,000 hospitalizations and 105 deaths.[3] Chickenpox is a more severe disease in adults, pregnant women, immunosuppressed individuals and children less than one year of age.[4] The risk of complications and death attributable to varicella can be up to 10- to 20- times higher for adults than for children.[5]

During the years (1990-1994) immediately preceding introduction of the vaccine, more than 90% of the infections, two-thirds of varicella-related hospitalizations and almost half of varicella-related deaths in the US occurred in children.[6] Post-licensure vaccine effectiveness studies have shown that the vaccine is highly effective in preventing severe disease and is 70% to 87% effective in preventing all disease.[7,8] Since introduction of varicella vaccine in the US in 1995, varicella cases and hospitalizations have declined approximately 80% in areas of the country where active surveillance for varicella is being conducted and where vaccine coverage reached 70% to 80% in 2000. Varicella cases declined in all age groups, including infants and adults with the greatest decline occurring among children one to four years of age. In the combined three surveillance areas, hospitalizations due to varicella declined from a range of 2.7 to 4.2 per 100,000 population in 1995 through 1998 to 0.6 and 1.5 per 100,000 population in 1999 and 2000, respectively.[9]

Risk of Vaccine Adverse Events

The majority of children who receive the varicella vaccine will have no adverse events. Adverse events that do occur are typically mild reactions such as injection site tenderness or swelling, fever and mild rash. Local reactions have been reported by 19% of children and by 24% of adolescents and adults.[10] Two cases out of 100,000 shots given may experience a serious reaction consisting of seizure caused by fever and pneumonia.[11]

A mild form of chickenpox may occur among vaccinees. Most of these cases occur in children and all cases have been without complications. The risk of developing disease from natural wild virus is four to five times higher than developing the disease from the vaccine.[10]

Cost-Benefit Analysis

A cost-effectiveness study, modeling the projected impact of vaccination and current direct and indirect costs, found a savings of $5.40 for every dollar spent on routine vaccination of preschool-age children. This is equivalent to a savings of $400 million in healthcare costs annually in the US.[12] Another model, using data from the National Health Interview Survey, the National Hospital Discharge Survey and the National Medical Expenditure Survey, determined the net economic benefit of varicella vaccination to be $6.6 million.[13] These studies found that the cost of a varicella vaccination program was equal to, or greater than, the direct medical cost of treating the disease if

GLOSSARY TERMS

Adverse events
Advisory Committee on Immunization Practices
Bacteria
Breakthrough cases
Cases
Chickenpox
Coverage
Disease
Encephalitis
Group A streptococcus
Hemorrhagic
Herpes zoster
Immunization
Immunocompromised
Immunosuppressed
Invasive
Pneumonia
Risk
Seizure
Shingles
Vaccine
Vaccine Adverse Events Reporting System
Vaccinees
Varicella
Virus

ACRONYMS

VAERS Vaccine Adverse Events Reporting System

WEB RESOURCES

VARICELLA:

National Partnership for Immunization
http://www.partnersforimmunization.org/chickenpox.html

Centers for Disease Control and Prevention's *Epidemiology and Prevention of Vaccine-Preventable Diseases (The Pink Book)*
http://www.cdc.gov/nip/publications/pink/varicela.pdf

National Center for Infectious Diseases
http://www.cdc.gov/ncidod/diseases/list_varicl.htm

National Network for Immunization Information
http://www.immunizationinfo.org/database/index.cfm

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/each_vaccine2a.shtml#name11

Immunization Action Coalition
http://www.immunize.org/varicella

VARICELLA VACCINE:

National Partnership for Immunization
http://www.partnersforimmunization.org/chickenpox.html

Recommendations of the Advisory Committee on Immunization Practices (ACIP)
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4806a1.htm

Vaccine Information Statement
http://www.cdc.gov/nip/publications/vis/vis-varicilla.pdf

VACCINE MANUFACTURER:

Merck Vaccine Division
http://www.merckshardpdohme.com/disease/preventable/cpox

indirect costs associated with the disease were not included in the analysis. Savings came from the difference in lost wages from parents caring for ill children as fewer children would contract varicella after immunization. Therefore, fewer parents would need to stay home to care for them.[14]

Safety Studies

- A study evaluated the vaccination of 89,753 children and adults for possible rare medical events associated with vaccination. The varicella vaccine was shown to display a favorable safety profile, free of serious side effects. In addition, rates of varicella-like rash were low, consisting of approximately 2.5 breakthrough cases per year.[15]
- Analyses of reports to the Vaccine Adverse Events Reporting System (VAERS) from March 17, 1995 through July 25, 1998 found that the vast majority of reported cases of vaccine reactions were not serious. VAERS received 6,574 case reports of adverse events in recipients of varicella vaccine, a rate of 67.5 reports per 100,000 doses. Approximately 4% of the reports described serious adverse events, including 14 deaths.[16]
- Mathematical models predict that if varicella vaccine coverage in children is more than 90%, a greater proportion of cases will occur at older ages, but the overall varicella disease burden will decrease for children and adults. However, if immunization rates for young children vaccinated with varicella vaccine remain relatively low, the number of children who become susceptible adults will increase as will the opportunities for susceptible adults to contract varicella from unimmunized children.[2]
- Fourteen pre-licensure studies were conducted on a total of 12,323 subjects aged six months to 17 years. Mild adverse events reported in these studies included injection site pain and redness, rashes and increased body temperature. Moderate events included rash, fever and swelling. The only reported serious adverse event attributed to the vaccine was herpes zoster or shingles.[12]

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VACCINES FOR SPECIAL RISK GROUPS AND TRAVELERS TO SELECTED GEOGRAPHICAL AREAS

Vaccines recommended for use by the general public are not the only vaccines currently available to help prevent the spread of infectious diseases worldwide. Many vaccines have been and are being developed for use by specific groups of people who, because of their health, working or living environment, travels or genetic background, are at increased risk of developing a particular disease. This section includes a discussion of vaccines available for some of these groups. As these vaccines have not been recommended for general use, weighing the benefits and risks of their use becomes especially important in evaluating their use in particular individuals.

Because of recent increased concern about the use of anthrax and smallpox as biological weapons, information on these diseases and the vaccines currently available to prevent them have been included. Neither vaccine is currently available for general use by the public in the US. Anthrax vaccine is available for use by military personnel and was made available to anthrax-exposed civilians during 2001-2002. In the absence of a confirmed case of smallpox and with the presumption that the risk of bioterrorist attack with smallpox is low, smallpox vaccine has been recommended for persons in the US predesignated by the appropriate bioterrorism and public health authorities to conduct investigation and follow-up of initial smallpox cases. Under these same circumstances, smallpox vaccine has also been recommended for some US healthcare personnel at risk of exposure to initial cases of smallpox in facilities that are predesignated to receive these patients.[1]

GLOSSARY TERMS

Anthrax
Cases
Disease
Risk
Smallpox
Vaccine

ANTHRAX

General Disease Information

Anthrax is an acute infectious disease caused by the large, spore-forming bacterium *Bacillus anthracis.* Anthrax spores are extremely resistant and can survive for 40 years in soil[2] and 80 years in a vial.[3] But more commonly, when significant microbial competition exists in the soil, anthrax contamination usually lasts only a few months and rarely for more than three or four years.[4] In infected animals or humans, *Bacillus anthracis* can replicate and release a endotoxin that causes the symptoms of anthrax. Animals are infected with anthrax when they ingest or inhale spores while grazing,[5] thus the disease is most common in herbivores, which become infected by ingesting spores from the soil.[6]

Naturally occurring disease in humans is acquired by skin contact, ingestion or inhalation of *Bacillus anthracis* spores from infected animal products or from inhalation of spores from the environment.[5] Anthrax is not contagious and therefore cannot be transmitted from one person to another. In humans, three types of anthrax infection can occur:

1. Cutaneous anthrax: Up to 2,000 cases of cutaneous anthrax occur worldwide in humans each year.[6] Most of these infections (about 95%) occur when the bacterium enters a cut or abrasion on the skin.[7] Infections begin as a raised itchy bump resembling an insect bite and progress to a fluid-filled blister with a black area in the center. Lymph glands may swell in the areas surrounding the blister.[8] While approximately 5% to 20% of untreated cases will result in death, such deaths are rare (<1%) when the infection is treated with the appropriate antimicrobial therapy. Only two cases of cutaneous anthrax arising from direct contact have been reported.[5]

2. Gastrointestinal anthrax: Although outbreaks have been reported in Africa and Asia, this form of anthrax is very uncommon. Gastrointestinal anthrax occurs when a person ingests insufficiently cooked, contaminated meat.[6] Infection results in an acute inflammation of the intestinal tract. Symptoms include nausea, vomiting, loss of appetite and fever followed by abdominal pain, vomiting of blood and severe diarrhea. The death rate for this form of anthrax is unknown but has been estimated to be between 25% and 60% of cases.[5]

3. Inhalational anthrax: This form of anthrax is acquired from environmental sources and occurs when 8,000 to 50,000 anthrax bacteria spores enter the body through the airways. After an incubation period of one to seven days, mild symptoms of fever, malaise, fatigue, cough and mild chest discomfort may develop. Mild symptoms will rapidly progress to respiratory distress and shock in another two to four days and is then followed by more severe symptoms, including breathing difficulty and exhaustion. Human-to-human transmission of inhalational anthrax has never been reported.[7] Before recent events, no case of inhalational anthrax had been reported in the US since 1978.[6] The case fatality rate of inhalational anthrax cases in 2001 with the use of intensive antibiotic and other therapy was 45%.[5]

Prior to September 11, 2001, the annual incidence of anthrax in the US had declined from 127 cases per year in the early years of the twentieth century to less than one case per year in the last 20 years.[8] The mortality rate of these cases of anthrax in the US was 89%, but the majority of cases occurred before the development of critical care units and, in some cases, before the introduction of antibiotics.[6]

Research on anthrax as a biological weapon began more than 80 years ago and today at least 17 nations are believed to have offensive biological weapons programs. It is uncertain how many of these countries are working with anthrax.[6] Inhalational anthrax is considered to be a bioweapon of interest to terrorists and one that is highly feared by civilians. Rough estimates of the potential effects of an attack suggest that the release of 100 kg (220 pounds) of anthrax spores by aerosol from a single airplane

GLOSSARY TERMS

Acute
Allergic reaction
Anthrax
Antibiotic
Bacillus anthracis
Bacteria
Booster
Cases
Clinical trials
Cutaneous anthrax
Disease
Endemic
Endotoxin
Erythema
Gastrointestinal anthrax
Immunization
Induration
Inhalational anthrax
Malaise
Nodules
Penicillin
Placebo
Prevalence
Reactogenicity
Risk
Scarification
Systemic
Vaccine

ACRONYMS

CDC	Centers for Disease Control and Prevention
FDA	Food and Drug Administration

WEB RESOURCES

Advisory Committee on Immunization Practices
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4915a1.htm

Centers for Civilian Biodefense Strategies
http://www.bt.cdc.gov/agent/anthrax/anthraxgen.asp

Center for Disease Control and Prevention
http://www.bt.cdc.gov/agent/anthrax/anthraxgen.asp

Department of Defense
http://www.anthrax.osd.mil/

University of Alabama at Birmingham's Bioterrorism Web Site
http://www.bioterrorism.uab.edu

VACCINE MANUFACTURER:
Bioport
http://www.bioport.com

could cause from one to three million casualties in a city the size of Washington, DC.[9] Other estimates have suggested the potential for 50% fatalities to occur as far as 160 km (100 miles) downwind from an aerosol release.[10] However, most experts agree that individuals or groups without access to advanced biotechnology would not be able to manufacture a lethal anthrax aerosol that could be inhaled.[6]

On October 4, 2001, the threat of anthrax as a biological weapon became a reality when a man in Boca Raton, Florida was diagnosed with and later died of inhalational anthrax. An additional four US citizens fell victim, and a total of 18 contracted either the inhalational or cutaneous form. The Centers for Disease Control and Prevention (CDC) has recommended ciprofloxacin and doxycycline as the preferred post-exposure treatment for cutaneous anthrax and combination therapy with more than one active agent against *Bacillus anthracis* for inhalational anthrax.[5] And since the first case of anthrax was diagnosed, an estimated 30,000 people (mainly federal employees) have received prophylactic antibiotics.[11]

Risk-Benefit Analysis of Vaccination

Anthrax vaccine was first licensed in the US in 1970 and is produced by Bioport Corporation in Lansing, Michigan (formerly Michigan Biologic Products Institute). The vaccine is a cell-free filtrate that is produced from a form of anthrax that does not cause disease.[6] Since its licensure, the anthrax vaccine has been safely administered to at-risk wool mill workers, veterinarians, laboratory workers, livestock handlers and the US military. The duration of protection from disease following vaccination is unknown. The US Army's anthrax vaccine program alone has inoculated more than 150,000 soldiers.[11]

A controlled clinical trial was conducted in a susceptible population working in four mills in the northeastern US where raw imported goat hair contaminated with *Bacillus anthracis* was used. The vaccine used was similar to the currently licensed US vaccine and was found to be 92.5% effective in protecting the population against cutaneous anthrax as compared with a placebo. No assessment of the effectiveness of the vaccine against inhalational anthrax could be made because there were too few cases.[8]

Approximately 30% of vaccinated men and 60% of vaccinated women will experience temporary reactions such as soreness, redness, itching, swelling and lumps at the site of injection. Muscle aches, joint aches, headaches, rash, chills, fever, nausea, loss of appetite, malaise or related symptoms will occur in 5% to 35% of persons vaccinated. Severe allergic reactions may occur in one out of 100,000 doses administered, and rare, serious events such as those requiring hospitalization occur once per 200,000 doses.[11]

Because of limited production capacity, the anthrax vaccine is not currently available for the general public. The only people currently receiving the anthrax vaccine are designated military units and personnel involved in anthrax research.

Treatment of Anthrax Infection

Anthrax is susceptible to antibiotics, including penicillin, tetracycline and oral fluoroquinolones (ciproflaxin and oflaxacin). The Federal Drug Administration (FDA) has approved quinolone ciprofloxacin (Bayer Corporation, West Haven, CT) and tetracycline doxycycline (Pfizer, Inc., New York, NY) as treatment options for anthrax. The antibiotics do not kill the bacteria but prevent them from replicating and releasing the deadly endotoxins that are the primary cause of death.[9] Prophylactic treatment with these antibiotics should be given to exposed individuals regardless of their anthrax vaccination status.[8]

Safety Studies

- In the former Union of Soviet Socialist Republics (USSR), 3,500 volunteers were vaccinated with anthrax vaccine from 1943 to 1950. Complete safety and a lack of local side effects were reported.[12]
- From 1951 to 1952, a field trial was conducted in 14 anthrax-endemic rural districts in the former USSR. A total of 141,663 individuals were vaccinated (92,150 by scarification and 49,513 by injection under the skin). Among those individuals who were vaccinated by injection under the skin, 5,402 experienced a rise in body temperature and local erythema. A slight induration at the site of injection occurred in 14 cases.[12]
- Follow-up of 110 US military personnel who had received the anthrax vaccine found that the prevalence of adverse reactions following immunization was 40%, which was higher than expected.[13]
- A study conducted to determine whether receipt of anthrax vaccination by reproductive-age women had an effect on pregnancy rates followed 385 pregnancies occurring after at least one anthrax vaccination in 3,136 women and 130 pregnancies in 962 unvaccinated women. Women who received the anthrax vaccine were 1.2 times as likely to give birth as unvaccinated women.[14]
- Studies on the safety of four lots of anthrax vaccine, including approximately 16,000 doses administered to approximately 7,000 participants, found that mild local reactions were reported in 3% to 20% of all doses, moderate reactions were reported in 1% to 3% of all doses and severe reactions in less than 1% of all doses.[7]
- From 1973 to 1999, 1,590 individuals working in the US Army Medical Research Institute of Infectious Diseases received 10,451 doses of anthrax vaccine. Under a passive reporting system, 4% of these doses produced a local reaction consisting of erythema, induration, itching and swelling at the site of injection. Systemic reactions consisting of fever, chills, malaise, muscle aches or joint aches occurred following 0.5% of doses. All local and systemic reactions resolved without any lost time from work or long-term effects.[5]
- Investigators from the US Army Medical Research Institute of Infectious Diseases assessed vaccine safety in previously vaccinated soldiers who were given a booster of anthrax vaccine as part of an actively monitored study. Of 486 subjects who received the anthrax vaccine, 21% had local erythema and/or induration. In 5%, the erythema and/or induration was 5 cm or more. No reaction caused lost time from work and all resolved.[5]

- A study of anthrax vaccine reactogenicity, conducted by the Canadian Armed Forces in 547 individuals who received the anthrax vaccine revealed mild local reactions after 10.1% of doses, moderate local reaction after 0.5% and systemic reactions occurred in 1.5%. No long-term effects nor serious local reactions were reported except for one individual reporting a persistent nodule at the local site and multiple nodules at several distant sites.[15]

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JAPANESE ENCEPHALITIS

General Disease Information

Japanese encephalitis (JE) is a viral infection transmitted mainly by the bites of a particular type of mosquito. JE is the leading cause of childhood encephalitis in Asia with approximately 35,000 cases and 10,000 deaths reported annually. Because the disease is often found in remote locations that are not conducting routine surveillance for JE, and because the great majority of infections are asymptomatic, official reports likely underestimate the true number of cases.[1] In endemic areas, children are at the greatest risk for developing this disease. Only one in 250 infections results in clinical disease such as encephalitis, high fever, headache, seizures and gastrointestinal symptoms. JE will lead to severe encephalitis in one in 20 to 1,000 cases. Of those who develop encephalitis, death occurs in up to 30% of cases.[2]

Risk-Benefit Analysis of Vaccination

The JE vaccine is 91% effective in preventing this disease and has been effective in reducing the number of cases of disease in Beijing and other parts of China where high JE immunization rates are maintained.[1,3] The risk of JE for short-term international travelers and for those who confine their travel to urban areas is very low.[2] Between 1981 and 1992 only 11 US residents became infected with JE virus; eight were military personnel or their dependents.[3] Expatriates and travelers who live in rural areas where JE is endemic or epidemic for prolonged periods are at the greatest risk for developing this disease. In addition, travelers with extensive outdoor and evening exposure in these areas might be at an increased risk of disease even if their trip is brief.[2]

No association has been found between this vaccine and serious vaccine-related neurological complications during the more than 30 years that the vaccine has been used. Approximately 20% of vaccinees will experience local tenderness, redness or swelling at the site of injection. Mild systemic symptoms, chiefly headache, low-grade fever, myalgias, malaise and gastrointestinal symptoms are reported in 10% to 30% of vaccinees.[1] However, information contained in the product insert for this vaccine warns that vaccinated persons should remain within access of prompt medical care for 10 days following immunization because of the rare but real possibility of a severe reaction.

Safety Studies

- After an outbreak of JE on Okinawa, Japan in 1945, 53,000 American soldiers stationed there received this vaccine. Eight neurological reactions were observed. However, similar cases were reported concurrently in nonvaccinated individuals, and it is unclear whether the illnesses were vaccine-related.[4]
- One case of Guillain-Barré syndrome, temporally related to JE immunization, was observed following immunization of approximately 20,000 American soldiers with the vaccine prior to US licensure.[1]
- Several anecdotal reports of severe neurological side effects following vaccination have been reported in Japan, Korea and Denmark, but no positive association between these reports and the vaccine have been made.[1]
- An early prospective study in Japan to detect vaccine-associated adverse events found no neurological complications occurring within a month after vaccination in 38,384 subjects receiving crude or purified vaccine.[5]
- A country-wide study in Japan to detect neurological complications found 26 temporally related cases between 1957 and 1966. Rates and comparisons with nonimmunized controls were not available.[1]

GLOSSARY TERMS

Advisory Committee on Immunization Practices
Association
Cases
Controls
Disease
Encephalitis
Endemic
Epidemic
Guillain-Barré syndrome
Immunization
Japanese encephalitis
Malaise
Myalgia
Risk
Seizure
Systemic
Vaccine
Vaccinees
Virus

ACRONYMS

JE	Japanese encephalitis

WEB RESOURCES

Advisory Committee on Immunization Practices Recommendations
http://www.cdc.gov/mmwr/preview/mmwrhtml/00020599.htm

Children's Vaccine Center
http://www.childrensvaccine.org/html/v_enceph_qf.htm

McKinley Health Center – University of Illinois at Urbana-Champaign
http://www.mckinley.uiuc.edu/health-info/dis-cond/vacimmun/jap-ence.html

National Center for Infectious Diseases
http://www.cdc.gov/travel/jenceph.htm

VACCINE MANUFACTURER:
Aventis Pasteur
http://www.aventispasteur.com

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RABIES

General Disease Information

Rabies is a viral infection transmitted to humans by a scratch or a bite of an infected animal or the transfer of the infected animal's saliva to a human mucous membrane (lining of nose or mouth, open wound, etc.).[1] Disease occurs after the rabies virus invades the victim's central nervous system, causing inflammation of the brain and spinal cord and rapid progression to paralysis, coma and death.[1] The disease is almost always fatal.[2] Worldwide at least 50,000 deaths occur each year.[3]

Rabies is found on all continents except Antarctica[1] and more than 2.5 billion people live in regions where rabies is endemic.[3] Although human rabies can be found in all age groups, cases are most common in persons younger than 15 years. The majority of rabies victims are male[4] and globally every yearmore than 10 million people receive post-exposure vaccination against this disease.[3] Almost one million emergency room visits for animal bites occur each year in the US (mostly from dogs and cats) and each case has to be evaluated as a possible rabies exposure.[5-7]

In the 1940s and 1950s, a marked decrease in the number of rabies cases among US domestic animals resulted in a substantial decrease in the incidence of rabies among humans in the US. In 1950, 4,979 cases of rabies were reported among dogs, and 18 cases were reported among humans. But between 1980 and 1997, only 95 to 247 rabies cases were reported each year among dogs and on average only two human cases were reported each year.[8] During this same period, 12 cases of human rabies in the US resulted from dog bites that were inflicted outside of the US ("imported cases").[9]

Meanwhile, rabies among wildlife—especially raccoons, skunks and bats—has become more prevalent since the 1960s, accounting for more than 90% of all cases of animal rabies reported to the Centers for Disease Control and Prevention (CDC) each year. Rabies among wildlife occurs throughout the continental US; only Hawaii remains consistently rabies-free.[10]

Since 1990, bats have become the major source of rabies transmission to humans in the US. Between 1990 and 2000, 32 cases of rabies in humans were reported. Seventy-five percent of these cases were caused by rabies virus transmitted by bats. Recognizing the significant role of bats in rabies transmission, the CDC has recommended that post-exposure treatment might be appropriate if the bat cannot be tested even if a bite, scratch or mucous membrane exposure from the bat is not apparent.[2] Cavers are considered to be at higher risk for rabies exposure than the general public due to their potential contact with bats and have been recommended since the 1960s to receive pre-exposure prophylaxis.[11]

Risk-Benefit Analysis of Vaccination

Rabies vaccine can be given either pre- or post-exposure. Pre-exposure vaccination eliminates the need for rabies immune globulin (RIG) and reduces the post-exposure vaccine regimen. It can protect against unapparent exposures, such as in children[12] or when treatment is delayed.[2] The vaccine induces an active immune response (rabies neutralizing antibodies) after seven to 10 days that usually lasts for two or more years. Because rabies exposures are rare and are always episodic, the general US population does not require pre-exposure vaccination.[2]

RIG is also a component of post-exposure treatment. RIG provides a rapid, passive immunity that persists for only a short time.[2] However, RIG is expensive. One proven rabid cat in New Hampshire in 1994 resulted in an expenditure of $1.1 million to provide at least 665 individuals with post-exposure treatment.[13] And although rabies among humans is rare in the US, approximately 16,000 to 39,000 persons receive post-exposure prophylaxis each year.[14]

GLOSSARY TERMS

Cases
Coma
Disease
Eczema
Encephalitis
Endemic
Erythema
Guillain-Barré syndrome
Immunization
Imported cases
Malaise
Meningitis
Multiple sclerosis
Prophylaxis
Rabies
Rabies immune globulin
Risk
Steroids
Systemic
Vaccine
Vaccinees
Virus

ACRONYMS

CDC	Centers for Disease Control and Prevention
RIG	Rabies immune globulin

WEB RESOURCES

Advisory Committee on Immunization Practices Recommendations
http://www.cdc.gov/travel/diseases/rabies.htm

National Center for Infectious Diseases
http://www.cdc.gov/ncidod/dvrd/rabies/

National Center for Infectious Diseases Travelers' Health
http://www.cdc.gov/travel/diseases/rabies.htm

National Institute of Allergy and Infectious Disease
http://www.niaid.nih.gov/factsheets/rabies.htm

VACCINE MANUFACTURER:

Aventis Pasteur
http://www.us.aventispasteur.com/vaccines/rabies/main.htm

Chiron
http://www.chiron.com

RabAvert® and Imovax® rabies vaccines are equally effective in providing protection from rabies disease and are generally well-tolerated. In studies with Imovax®, 30% to 74% of rabies vaccinees experienced local reactions, such as pain, erythema and swelling or itching at the site of injection. Systemic reactions, such as headache, nausea, abdominal pain, muscle aches and dizziness have been reported among 5% to 40% of Imovax® recipients.[15]

Severe and life-threatening neurological adverse events are rare after receiving RabAvert® or Imovax® rabies vaccines. For instance, against a background of 11.8 million doses of RabAvert® rabies vaccine distributed worldwide, 10 cases of encephalitis or meningitis, seven cases of temporary paralysis, including two cases of Guillain-Barré syndrome, one case of myelitis, one case of neurologic disease and two cases of suspected multiple sclerosis were temporally associated with the rabies vaccine RabAvert®.[16] Three cases of neurological illness resembling Guillain-Barré syndrome that resolved without secondary problems in 12 weeks, and a focal subacute central nervous system disorder temporally associated with Imovax® have been reported.[15]

Cost-Benefit Analysis

A pharmaeconomic study on pre-exposure rabies immunization indicated that the CDC's recommendation to serologically test for rabies following possible exposure coupled with the use of vaccine will yield a cost savings for those who should maintain an adequate rabies antibody level due to their vocation or activities.[17]

According to existing documented economic evaluations in the US, only two individuals per 1,000 exposed persons need to be at risk of contracting bat rabies for it to be economical to give post-exposure prophylaxis to all of the exposed persons.[18]

Safety Studies

- In a Phase III post-exposure (1,252 patients) and pre-exposure (37 patients) clinical study in India from 1985 to 1993, RabAvert® vaccine was well-tolerated in all age groups among the 1,289 vaccinees. Forty patients (3.2%) complained of mild to moderate pain or tenderness at the site of injection that lasted for one to two days. Six (0.5%) patients developed mild temperatures lasting 12 to 24 hours . Two (0.2%) patients developed a mild rash lasting 24 to 28 hours and two (0.2%) patients developed a generalized eczema that was controlled using steroids.[19]
- In a pre-exposure study of normal volunteers who were vaccinated against rabies using the two human rabies vaccines available in the US (RabAvert® and Imovax®), pain at the site of injection was the most common local adverse reaction (34% and 45%, respectively) and the most common systemic adverse reactions were malaise (15% and 25%, respectively), headache (10% and 20%, respectively) and dizziness (15% and 10%, respectively).[16]

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SMALLPOX

General Disease Information

Smallpox is an acute infectious disease caused by the variola virus. This disease spreads most easily during cool, dry winter months but can be transmitted in any climate and in any part of the world.[1] Initial symptoms of high fever of 101 degrees Fahrenheit or higher, chills, abdominal pain, vomiting, fatigue and head and back aches usually appear about 12 days after exposure to the virus. A characteristic rash, usually seen on the face, arms and legs, develops one to four days later. The rash then develops into pus-filled lesions that eventually scab and fall off after three to four weeks.[2]

Smallpox is contagious and spreads from person to person by infected saliva droplets. Before vaccine became available, almost everyone throughout the world contracted smallpox, including George Washington[3] and Abraham Lincoln.[4] Spread of smallpox throughout the population was generally slower than for other infectious diseases such as measles or chickenpox. Because smallpox is not contagious until immediately before the appearance of a rash on the infected person, the disease was spread primarily to household members and friends, and large outbreaks were uncommon. Infected persons are most contagious during the first week following the onset of rash.[5]

Two major forms of the disease, variola major and variola minor, exist. Variola major is the more severe form of smallpox and consists of four main clinical presentations. These include ordinary, modified, flat and hemorrhagic. Ordinary smallpox occurs among 90% or more of the unvaccinated persons who contract smallpox. Modified smallpox is a less severe form of disease that occurs mostly in previously vaccinated persons. This form of smallpox disease is rarely fatal. Flat smallpox is characterized by flat lesions and severe disease. Hemorrhagic smallpox is a severe yet uncommon form of smallpox disease that is accompanied with extensive internal bleeding. Most cases of flat and hemorrhagic smallpox are fatal.[2]

While the majority of patients who were infected with smallpox recovered, variola major epidemics resulted in death rates of 30% of infected, unvaccinated persons. Epidemics of the milder variola minor form of smallpox resulted in death rates of 1% or less of infected, unvaccinated persons.[2]

Smallpox was probably first used as a biological weapon during the French and Indian Wars of 1754-1767 when British forces in North America distributed blankets that had been used by smallpox patients to Native Americans collaborating with the French. As many as 50% of those exposed are believed to have died.[6] Development of a smallpox vaccine by Edward Jenner in 1796 ultimately led to the World Health Organization's (WHO) declaration of worldwide smallpox eradication in 1977 and elimination of the threat of natural infection by the smallpox virus.[6]

Routine vaccination of children in the US was discontinued in 1971 with the recognition that the risks of vaccination complications exceeded the essentially zero risk of acquiring smallpox. In 1980, the World Health Assembly recommended that all countries cease smallpox vaccination. WHO also recommended that all laboratories destroy their stocks of smallpox virus or transfer them to one of two WHO reference laboratories - the Institute of Virus Preparations in Moscow, Russia, or the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, US. All countries reported compliance.[2]

The eradication of smallpox cost approximately US $313 million over 10 years, an investment which has been paid back many times over in savings in vaccines and medical care and the suspension of international surveillance activities.[7] The savings, as a result of the cessation of vaccination and quarantine measures, was estimated to be in excess of $1 billion annually.[8]

Currently, there is no evidence of smallpox transmission anywhere in the world. It is not known what type of materials may have been produced by bioweapons laboratories that worked with smallpox virus prior to or after 1980, or if smallpox

GLOSSARY TERMS

Acute
Adverse events
Advisory Committee on Immunization Practices
Blood serum
Cases
Case series
Chickenpox
Clinical trials
Controls
Disease
Eczema
Efficacy
Encephalitis
Epidemic
Immunization
Immunocompromised
Placebo
Risk
Serum
Smallpox
Systemic
Vaccine
Vaccinees
Vaccinia virus
Variola virus
Virus

ACRONYMS

ACIP	Advisory Committee on Immunization Practices
AIDS	Acquired Immune Deficiency Syndrome
CDC	Centers for Disease Control and Prevention
HIV	Human Immunodeficiency Virus
VIG	Vaccinia immune globulin
WHO	World Health Organization

WEB RESOURCES

Advisory Committee on Immunization Practices (ACIP)
http://www.cdc.gov/nip/acip/default.htm

Center for Civilian Biodefense Strategies
http://www.hopkins-biodefense.org/pages/agents/agentsmallpox.html

Centers for Disease Control and Prevention
http://www.bt.cdc.gov/agent/smallpox/smallpoxgen.asp

University of Alabama at Birmingham's Bioterrorism Web site
www.bioterrorism.uab.edu

VACCINE MANUFACTURER:
Acambis
http://www.acambis.com

virus from such facilities was destroyed or submitted to the WHO reference laboratories. However, according to recent smallpox vaccination recommendations made by the Advisory Committee on Immunization Practices, the threat of an attack on the US using a smallpox virus has been assessed as low.[9]

Risk-Benefit Analysis of Vaccination

The only weapons against smallpox are vaccination and patient isolation.[1] Smallpox vaccine contains vaccinia virus, which is in the same family as variola virus (the virus that causes smallpox disease). However, vaccinia virus is genetically distinct from variola virus and its use in vaccines precludes vaccinees from developing or transmitting smallpox, while developing immunity to that disease.[2]

More than 95% of first-time vaccinees will develop detectable antibodies against smallpox disease. Smallpox vaccine efficacy has never been measured precisely in controlled trials but studies have shown a 91% to 97% reduction of disease among vaccinees who were later exposed to a smallpox patient in their household.[2]

Three to five days following vaccination with vaccinia, a lesion develops at the site of inoculation. Once healed, this lesion leaves a permanent scar at the immunization site. The lesion/scar is an indication that viral replication has taken place and that the vaccination was successful. In addition, vaccination can produce minor reactions in vaccinees, including vaccination site swelling and tenderness up to two to four weeks after the lesion has healed. Approximately 70% of children will experience at least one day of fever of 100 degrees Fahrenheit or more for 4 to 14 days following vaccination.[2]

The most frequent complication of smallpox vaccination is the transfer of vaccinia from the vaccination site to another part of the body, most commonly the face, eyelid, nose, mouth genitalia and rectum. Most of these lesions heal without specific treatment. Moderate and severe complications of smallpox vaccination also can occur. A localized or systemic dissemination of vaccinia may occur in persons with a history of eczema. One out of every 4,000 primary vaccinations will result in rash. Progressive vaccinia in immunocompromised individuals, that frequently results in death, occurs in one out of every 600,000 primary vaccinations. Post-vaccination encephalitis, occurring in one vaccinee per 80,000 primary vaccinations, will lead to death in 15% to 25% of affected vaccinees and permanent neurologic disease in 25% of affected vaccinees. Although fewer than 50 cases have been reported, fetal vaccinia infection can result in a stillbirth or death of the infant following delivery. Death among vaccinees occurs in one out of 1,000,000 primary vaccinations and one out of 4,000,000 revaccinations.[2]

Despite these complications, vaccination has successfully and safely been administered to persons of all ages. Before 1972, smallpox vaccination was recommended for all US children at one year of age. Routine vaccination in the US stopped in 1972. It is likely that the immune status of those who were vaccinated more than 29 years ago has waned; however, previously vaccinated persons would be expected to exhibit an accelerated immune response if re-vaccinated or exposed to the smallpox virus.[5]

Immunization post-exposure to smallpox has been shown to offer some protection against the disease. Studies in Pakistan and India have shown that cases of smallpox among household contacts of smallpox patients who were vaccinated post-exposure were reduced by 91%. The lowest disease rates among these household contacts was found in those vaccinated less than seven days following exposure. Post-exposure vaccinees who did contract smallpox disease generally experienced a less severe form of disease.[2]

When this vaccine was routinely used in the US, complications associated with it were high. Potential adverse reactions included severe skin reactions, spread of the vaccine virus to other parts of the body and spread of the vaccine virus to other people. Rarely (about one case per 300,000 vaccinations), a vaccine-related brain infection occurred. During the US smallpox vaccination program, approximately seven to nine deaths per year were attributed to vaccination, with the highest risk for death in infants. Most of these infant deaths were attributed to postvaccination encephalitis.[14] Most primary vaccinations in the US were administered to children, so less is known about adverse events in adults.[15]

Vaccinia immune globulin (VIG) was once given following vaccination to protect those who needed vaccination but were at risk of experiencing vaccine-related complications. The Advisory Committee on Immunization Practices (ACIP) now recommends that VIG be reserved for treatment of vaccine complications with serious clinical manifestations. It has been estimated that if one million persons were vaccinated, as many as 250 would experience adverse reactions of the type that would require administration of VIG. Presently available supplies of VIG, also maintained by the CDC, are very limited in quantity. However, VIG can be obtained from the blood serum of persons one week following smallpox vaccinations. Therefore, VIG supply could be replenished with the reintroduction of smallpox vaccination.[5]

Transmission of vaccinia may occur when a recently vaccinated person has contact with a susceptible person. Among the participants of the CDC 10-state survey of complications of smallpox vaccination, the risk of transmission to contacts was 27 infections per one million total vaccinations; 44% of these contact cases occurred among children five years of age and younger.[14]

Such transmission is very dangerous when it involves individuals at high risk for developing severe reactions from the vaccine. These individuals include persons with eczema, the immunocompromised (including organ transplant recipients, HIV or AIDS patients and cancer patients) and pregnant women. A recent study has estimated that 15% of the US population would fall into one of these categories and therefore should not receive the smallpox vaccine. In addition, close contacts of these persons (another 10% of the US population) should also not receive the smallpox vaccine in order to avoid accidental transmission and subsequent severe reactions in the high risk persons.[16]

In the absence of a confirmed smallpox case and given the low risk of attack, smallpox vaccine has only been recommended for persons predesignated by the appropriate bioterrorism and public health authorities to conduct investigation and follow-up of initial smallpox cases as well as for healthcare personnel at risk of exposure to initial cases of smallpox in facilities that are predesignated to receive these patients.[10]

In the event that a smallpox outbreak would occur, smallpox vaccine is currently available and more vaccine doses are on their way. Approximately 15 million doses of vaccine were produced

by Wyeth Laboratories, Lancaster, PA in the 1970s and are currently stockpiled in the US.[11] A study evaluating the effectiveness of diluted smallpox vaccine found that these doses could be diluted significantly and still provide protection.[12] In addition, Aventis Pasteur has provided the government with 80 million doses of potent vaccine from their storage facilities. According to the CDC, enough smallpox vaccine will be available for everyone in the US by the end of 2002.[13]

Safety Studies

- A recent study estimated that vaccinating all persons aged 1 to 65 years of age in the US would result in approximately 4,600 serious adverse events and 285 deaths. This estimation excluded all high-risk individuals and their contacts.[16]
- No randomized controlled clinical trials have been performed to evaluate how effective the smallpox vaccine was in preventing disease in patients who suffered smallpox vaccine complications. Smallpox vaccination protocols were developed based on data consisting of case series and anecdotal reports, as well as controlled data suggesting that VIG may modify smallpox vaccine virus infection if administered at the same time as the vaccine.[15]
- Limited data support the efficacy of VIG in helping to prevent the development of smallpox following exposure to the disease. In a trial conducted in Madras, India, 705 family contacts of 208 smallpox patients were randomized to receive smallpox vaccine or smallpox vaccine plus VIG as soon as possible after the patient was admitted to the hospital. Smallpox developed in 5 of 326 contacts who received VIG compared with 21 of 379 controls, for a relative efficacy of 70% in preventing natural smallpox.[15]
- The potential for VIG to prevent post-vaccine encephalitis when administered with vaccine was studied among Dutch military recruits. More than 106,000 recruits received either VIG plus smallpox vaccine or placebo plus smallpox vaccine. Three cases of smallpox vaccine-associated encephalitis occurred in the VIG group compared with 13 cases of encephalitis in the placebo group.[17]

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TYPHOID FEVER

General Disease Information

Typhoid fever is an acute generalized infection that is caused by the bacterium *Salmonella typhi*. Severe forms of the disease are characterized by persistent high fever, abdominal discomfort, malaise and headache. Worldwide, an estimated 16 million cases of typhoid fever and 600,000 related deaths are reported.[1] Transmission of typhoid fever occurs in areas where sanitation is primitive and where water supplies are not treated. In such situations, human fecal material can contaminate water supplies.[2]

Prior to the introduction of antibiotics, this much-feared disease ran its course over several weeks and caused death in 10% to 20% of cases. But with the introduction of water treatment in the 20th century, the incidence of typhoid fever significantly decreased in large US cities. Typhoid fever remains endemic in most of the less-developed areas of the world, including parts of Africa, Asia and Latin America, where fecal contamination of water sources still occurs. This disease remains the main intestinal disease threat faced by children in developing countries after they have survived a plethora of diarrheal and dysenteric infections (all of which are not currently preventable by vaccines) during their first five years of life.[2]

Risk-Benefit Analysis of Vaccination

The three populations that are at particularly high risk of developing typhoid fever are children in endemic areas, travelers and military personnel from industrialized countries who visit endemic areas in developing countries and clinical microbiology technicians.[2] Between 1992 and 1994, an estimated 2.6 cases of typhoid fever per one million US international travelers were reported. However, since 1990, *Salmonella typhi* in Asia and northeast Africa have increasingly been resistant to many clinically relevant antibiotics.[2] The two typhoid fever vaccines licensed for use in the US (Vi polysaccharide and Ty21a typhoid fever vaccines) provide protection against disease in 50% to 80% of vaccinees.[1]

Local reactions are the most frequently reported adverse reactions for the Vi polysaccharide typhoid fever vaccine. Fever has been reported in up to 1% and headache in up to 3% of vacinees. The side effects of the Ty21a typhoid fever vaccine are rare and consist mainly of abdominal discomfort, nausea, vomiting and rash. Up to 5% of vaccinees have reported fever and headache.[1]

Safety Studies

- Controlled Phase II trials in US adults reported local reactions, including pain and tenderness at the injection site as the most common adverse events of the Vi polysaccharide vaccine.[3-4]
- Rates of adverse reactions in the vaccine recipients of three studies assessing the safety of the Ty21a typhoid fever vaccine were not significantly higher than those for the placebo group for any sign or symptom. [5-7]
- Large-scale field trials of 550,000 school children in Chile and 32,000 in Egypt as well as 32,000 persons ages three years to adulthood in Indonesia using Ty21a typhoid vaccine have not identified any vaccine-related adverse reactions.[7-12]

GLOSSARY TERMS

Acute
Adverse events
Antibiotic
Cases
Disease
Dysenteric infections
Endemic
Malaise
Placebo
Polysaccharide
Polysaccharide vaccine
Risk
Salmonella typhi
Typhoid fever
Vaccine
Vaccinees

WEB RESOURCES

Division of Bacterial and Mycotic Diseases
http://www.cdc.gov/ncidod/dbmd/diseaseinfo/typhoidfever_g.htm

National Center for Infectious Diseases
http://www.cdc.gov/travel/diseases/typhoid.htm

VACCINE MANUFACTURERS:

Aventis Pasteur
http://www.aventispasteur.com

Berna Products
http://www.bernaproducts.com

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YELLOW FEVER

General Disease Information

Yellow fever is a disease caused by a RNA virus transmitted to humans by mosquitoes or ticks.[1] The severity of this disease ranges from flu-like symptoms to severe hepatitis and hemorrhagic fever.[2] This disease kills an estimated 30,000 people per year and occurs only in sub-Saharan Africa, where the majority of cases are reported, and in tropical South America.[2,3] In Africa, 23% of yellow fever cases in infants and children will result in death. But in South America, cases occur primarily in young men and approximately 65% of cases die.[1]

Although yellow fever has rarely occurred in travelers, the disease has caused serious, life-threatening infections in unvaccinated international travelers.[4] In March 2002, a previously healthy, unvaccinated Texan died from yellow fever disease he contracted during a fishing trip in Brazil. During his trip, this 47 year-old man slept aboard an air-conditioned fishing boat and wore DEET insecticide-impregnated clothing while fishing.[5]

Risk-Benefit Analysis of Vaccination

Vaccination is the most efficient preventive measure against this disease, and the yellow fever vaccine is highly effective.[1,4] Some researchers believe that the risk of unvaccinated travelers developing yellow fever is probably increasing because potential yellow fever transmission zones are expanding to include urban areas with large populations of susceptible humans and abundant mosquitoes that can transmit the disease.[6]

No placebo-controlled trial has ever been performed to assess adverse reactions associated with this vaccine.[1] However, reported reactions to the yellow fever vaccine have been generally mild. Up to 5% of persons vaccinated against yellow fever have mild headaches, muscle pain, low-grade fevers or other minor symptoms for five to 10 days.[7] A review of reports submitted to the Vaccine Adverse Events Reporting System (VAERS) in the US from 1990 to 1997 found that anaphylaxis characterized by rash, hives and/or asthma, is uncommon after yellow fever vaccination, and occurs at a rate of one per 131,000 vaccine doses (this adverse event occurred principally among persons with histories of egg allergy[6]).[8] Of an estimated 54 million doses of vaccine that were administered in Brazil from 1996 through 2001, only two cases of serious adverse events were reported.[3] However, at the June 2001 meeting of the Advisory Committee on Immunization Practices (ACIP), seven cases of multiple organ system failure in recipients of the yellow fever vaccine between 1996-2001 were discussed. All seven persons became ill within two to five days of vaccination and required intensive care; six died.[6]

Safety Studies

- A study utilizing VAERS data found that the rate of reported adverse events following yellow fever vaccination among elderly persons was higher than among persons 25 to 44 years of age. The rate of systemic illness requiring hospitalization or leading to death after yellow fever vaccination was 3.5 per 100,000 among people 65 to 75 years of age and 9.1 per 100,000 for people 75 years of age and older.[4]
- Reactogenicity to yellow fever vaccine was monitored in 10 clinical trials conducted between 1953 and 1994. Self-limited and mild local reactions and systemic reactions (headache, headache and fever, and fever without symptoms) occurred in a minority of subjects five to seven days after immunization.[1]

GLOSSARY TERMS

Adverse events
Advisory Committee on Immunization Practices
Allergy
Anaphylaxis
Asthma
Cases
Clinical trials
DEET
Disease
Hemorrhagic fever
Hepatitis
Immunization
Placebo
Reactogenicity
Ribonucleic acid
Risk
Systemic
Vaccine
Vaccine Adverse Events Reporting System
Virus
Yellow fever

ACRONYMS

ACIP	Advisory Committee on Immunization Practices
DEET	N,N-diethyl-m-toluamide
RNA	Ribonucleic acid
VAERS	Vaccine Adverse Events Reporting System

WEB RESOURCES

Advisory Committee on Immunization Practices Recommendations
http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/00001620.htm

Division of Vector-Borne Infectious Diseases
http://www.cdc.gov/ncidod/dvbid/yellowfever/index.htm

National Center for Infectious Diseases
http://www.cdc.gov/travel/yelfever.htm

VACCINE MANUFACTURER:
Aventis Pasteur
http://www.aventispasteur.com

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VACCINE SAFETY ISSUES

Vaccine Safety Issues

Autism

Autism is a permanent, developmental disability that occurs in all racial, ethnic and social groups and falls into a disease category known as autism-spectrum disorders (ASD). Other ASDs include Asperger's disorder, childhood developmental disorder and pervasive developmental disorder not otherwise specified. Autism is characterized by problems with social interactions, difficulties with communication and by restrictive or repetitive interests and behaviors. The severity of autism can vary among individuals, ranging from poor language and daily living skills, to those who can function well in most settings.[1] Approximately 66% to 89% of individuals with autism also suffer from mental retardation.[2]

Autism is typically diagnosed between 18 to 30 months of age. Some children (approximately 20%) progress through a period of normal development before the onset of symptoms and may subsequently lose some of their earlier acquired skills. No blood or other medical test is available to diagnose autism, and a correct diagnosis depends on extensive, accurate analysis of a child's behavior and developmental history.[3]

A hypothesized link between autism and the measles, mumps and rubella (MMR) vaccine has been refuted by many public health experts and agencies, including the British Medical Research Council,[4] the World Health Organization,[5] the American Medical Association,[6] the American Academy of Pediatrics (AAP)[7] and the Institute of Medicine (IOM)[8] as well as numerous scientific studies.[9-14] This hypothesis was first proposed in 1998 in a small study of 12 children who were referred to a pediatric gastroenterology unit with histories of normal development followed by loss of acquired skills, diarrhea and abdominal pain. All research subjects except one were diagnosed with ulcerative colitis, a form of inflammatory bowel disease (IBD), and eight of the 12 subjects were diagnosed with autism.[15] The investigators proposed that the MMR vaccine might, within 24 hours to a few weeks of immunization, lead to intestinal abnormalities, which in turn could cause impaired intestinal function, allowing toxic intestinal products to reach the brain and cause neurological damage leading to autism. However, researchers explicitly stated that their findings did not prove an association between MMR vaccine and the syndrome they described.[15]

Temporal relationship?

Any evaluation of a temporal relationship between immunization with MMR vaccine and the development of autism must keep in mind that because MMR is administered at the age when many children are diagnosed with autism, it would be expected that most children, regardless of whether or not they have autism, would have received the MMR vaccine. It would be likely that many of the children with autism would have received the vaccine close to the time of their autism diagnosis.[16]

However, two questions need to be considered when assessing whether a temporal relationship exists between MMR vaccination and autism:

(1) Did symptoms of autism develop in children following immunization with the MMR vaccine?

Commentary following the publication of the 1998 study[15] noted that the disease of autism was known well before the MMR vaccine became available and that behavioral changes were almost always preceded by bowel symptoms.[17] A recent report by the AAP that analyzed over 1,000 references in the medical literature notes that most studies of the size and structure of the brains of ASD cases suggest that atypical brain development characteristic of the disease occurs before birth.[7]

At the time the 1998 study was conducted, about 90% of children in the UK had received the MMR vaccine.

Another research group in the United Kingdom attempted to replicate the findings of the 1998 study. These researchers noted a slightly increased relative risk for the association of MMR vaccination and initial parental concern about their child's

GLOSSARY TERMS

Acute
Adverse events
Asperger's disorder
Association
Autism
Autism-spectrum disorder
Bias
Blinded
Cases
Cerebral palsy
Childhood developmental disorder
Chronic
Congenital rubella syndrome
Control
Coverage
Crohn's disease
Disease
Dose-response relationship
Dysfunction
Encephalopathy
Enterocolitis
Fragile X syndrome
Gastroenterology
Gastrointestinal system
Gastrointestinal tract
Genome
HOXAI
Ileal-lymphoid-nodular hyperplasia
Immunization
Incidence
Inflammatory bowel disease
In situ hybridization
In utero
Institute of Medicine
Lymphocytes
Major histcompatibility complex
Measles
Metabolic disorders
MMR vaccine
Morbidity
Mumps
Neuropeptides
Neurotrophins
Nodules
Pervasive developmental disorder
Polymerase chain reaction
Prevalence
Registry
RNA
Risk
Rubella
Seizure
Selection bias
Temporal relationship
Thalidomide
Ulcerative colitis
Vaccine
Vaccination registry
Virus

ACRONYMS

AAP	American Academy of Pediatrics
ASD	Autism-spectrum disorder
HMO	Health maintenance organization
IBD	Inflammatory bowel disease
IOM	Institute of Medicine
MHC	Major histocompatibility complex
MMR	Measles, mumps, rubella
NCES	National Childhood Encephalopathy Study
NIH	National Institutes of Health
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
RNA	Ribonucleic acid

WEB RESOURCES

AUTISM:

National Partnership for Immunization
http://www.partnersforimmunization.org/issues.html

National Immunization Program
http://www.cdc.gov/nip/vacsafe/concerns/autism/default.htm

Johns Hopkins University Institute for Vaccine Safety
http://www.vaccinesafety.edu/cc-mmr.htm

National Network for Immunization Information
http://www.immunizationinfo.org

(continued)

development. However, researchers questioned whether this association may have resulted from the parents' difficulty in recalling the precise age at onset and hence they may have approximated that their child was 18 months of age when they first became concerned.[11] Researchers then conducted a further analysis of this proposed association and found no significant difference in the age at parental concern between children receiving MMR vaccine before the age of 15 months, those receiving vaccine at 15 months of age or later and those not receiving MMR vaccine.[18]

A study conducted in Sweden involving 55 known cases of autism compared autism prevalence rates in populations of children from two communities. The results indicated no difference in autism prevalence between children born after the introduction of the MMR vaccine in Sweden and those born before the vaccine was used.[10]

Before 1980, the majority of parents reporting to the Autism Research Institute stated that their children had autistic symptoms in early infancy. After 1980, over two thirds of the parents reported that their children's symptoms started after age 18 months.[19] The question remains whether this change in reporting of onset of disease is real or biased.

Rates of bowel problems and behavioral regression were compared in children who received the MMR vaccine before their parents became concerned about their development with those of children who either received the vaccine after their parents became concerned or did not receive the vaccine at all. No significant difference between these groups was found.[20]

The United Kingdom's National Childhood Encephalopathy Study (NCES) in 1976-1978 examined 770 cases of children with encephalopathy who previously appeared to be neurologically normal, to ascertain the relationship between immunization and various acute encephalopathic illnesses. Only 16 of these children had received measles vaccine within 7-14 days before the onset of their illness. When children with seizures accompanied with fever were excluded, the findings showed no significant association between measles vaccination and the onset of acute neurological events in previously healthy children.[21]

(2) Has there been an increase in the number of autism cases since the MMR vaccine was licensed?

According to a study done in the United Kingdom, the number of known autism cases has been increasing since 1979, and no sharp increase in cases was observed after the introduction of MMR vaccine in 1988. Among affected individuals, the age at diagnosis was similar whether the child had been vaccinated before or after age 18 months or had not been vaccinated.[11] If MMR vaccine was causing autism, it would be expected that children vaccinated at a younger age would develop autism at a younger age than children vaccinated at older ages.[9]

A recent AAP report noted that the increase in reporting of autism-spectrum disorders in recent years occurred long after the introduction of the MMR vaccine in the US in 1971.[7]

A review of 16 studies in North America, Europe and Japan found no evidence of an increase in autism rates following the introduction of the MMR vaccine.[22]

No change in the proportion of autistic children in the United Kingdom with bowel problems or developmental regression was found over a 20-year period beginning in 1979. This was the period of time when MMR vaccination was introduced in the United Kingdom.[19]

Strength of association?

The findings of the 1998 United Kingdom study described a striking and consistent pattern of ileal-lymphoid-nodular hyperplasia, an abnormality of the mucosal surface of the gastrointestinal tract, in nine of the 12 children examined.[15] The uniformity of these findings combined with the absence of detectable neurological

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccie.chop.edu/concerns.shtml#question7

Immunization Action Coalition
http://www.immunize.org/autism

National Alliance for Autism Research
http://www.naar.org

Institute of Medicine's Measles-Mumps-Rubella Vaccine and Autism Report
http://www.iom.edu/imsafety

abnormality in these children led the researchers to believe that some outside factor was causing the abnormal brain function. However, other investigators suggested that selection bias may have occurred in this study as the report was based on cases referred to a group known to be specifically interested in studying the possible relationship between MMR vaccine and IBD.[16] Such groups or centers are more likely to encounter patients with gastrointestinal disease. A more objective way to determine the prevalence of gastrointestinal symptoms in ASD patients is to evaluate all children with ASD in a particular community.[7]

Dose-response relationship?

If evidence was found that rates of autism were increasing relative to increased use of MMR vaccine, this information would suggest a possible dose-response relationship between MMR use and the development of autism. MMR immunization coverage rates among children born in 1980-1994 and enrolled in California kindergartens were recently compared to the number of autistic children enrolled in the California Department of Developmental Services regional service center system. The increase in the number of autism cases during this time period (373% relative increase) was substantially greater than the increase in MMR immunization coverage rates (14% relative increase). These substantially different increases do not provide evidence to support a causal relationship between the use of MMR and the development of autism.[13]

Data from the United Kingdom general practice research database were used to analyze the relationship between MMR vaccination and the diagnosis of autism in boys over time. Autism incidence rates increased almost fourfold among two to five year old boys born in each year from 1988 to 1993, while the prevalence of MMR vaccination remained relatively steady at over 95% for each year studied.[23] In another United Kingdom study, high, stable MMR immunization rates were observed during a period in which autism incidence was apparently increasing. Also, MMR vaccination coverage among autistic children at age two was found to be nearly identical to that of non-autistic children of the same age in the same London districts. These findings suggest an absence of a dose-response relationship between vaccine coverage and autism.[9]

Replication of findings?

Recent reports from both the IOM Immunization Safety Review Committee and AAP have not found evidence to support the hypothesis that the MMR vaccine causes autism at the population level.[7, 8] Both reports noted that existing epidemiological research shows no overall association between the MMR vaccine and autism. The IOM report did not exclude the possibility that the MMR vaccine could contribute to rare cases of ASD in a very small number of affected children.[8]

Data from a surveillance system created in 1982 when MMR vaccine was first introduced in Finland were analyzed for adverse events associated with MMR vaccination. Comprehensive analysis of 1.8 million individuals and consumption of almost three million vaccine doses during a 14-year follow up revealed no cases of autism, ulcerative colitis, Crohn's disease or any other chronic disorder affecting the gastrointestinal system.[14]

All 498 known cases of ASD among children living in certain districts of London who were born in 1979 or later were evaluated relative to an independent vaccination registry. An association between MMR vaccine and autism could not be identified.[9]

No association was found between IBD and autism in 325,000 French school-age children[24] or in nearly 9,000 children and adolescents at a London psychiatric care center.[25]

Biologic plausibility?

The 1998 British study identified an abnormal pattern of ileal-lymphoid-nodular hyperplasia in nine of the 12 autistic children examined.[15] However, any suggestion that MMR vaccine causes autism requires consideration of at least two additional biologic mechanisms. First, MMR vaccine must be shown to cause the observed intestinal abnormalities. Although nine of the 12 vaccinated children studied displayed this abnormality, suggesting an association between these two factors, this observation does not provide evidence that the MMR vaccine was the cause of the dysfunction. A biologic mechanism explaining how MMR vaccine might cause this intestinal abnormality has yet to be identified.

Studies of the biological plausibility of whether MMR use causes autism have focused on attempting to detect measles virus in the intestines of autistic MMR-vaccinated children along with an absence of measles virus in the intestines of non-autistic vaccinated children. Intestinal biopsy samples were tested for the presence of measles virus genome from children both with and without autism. Measles virus was detected in these samples using the techniques of polymerase chain reaction (PCR) and *in situ* hybridization. Seventy-five out of the 90 children with autism were found to have fragments of measles virus in their biopsies while only five out of the 70 children without autism had fragments of measles virus in their biopsies. No information was given by study authors about the immunization status of all 160 children who participated in this study, the length of time post-immunization (for those who had been immunized) that these samples were collected, nor whether the measles virus found in these samples was natural measles virus or vaccine virus, making it difficult to determine if MMR vaccine was associated with this finding. No information was given about whether laboratory personnel performing these tests were blinded as to the diagnosis (autistic or not autistic) of the child associated with each sample.[26] Blinding of laboratory research staff relative to patient status is a key practice necessary for assuring objectivity in clinical research.

Further studies are needed to determine whether the measles vaccine virus can be found in the intestines of autism cases after vaccination with MMR and whether finding measles vaccine virus in the intestine after immunization is abnormal.[7, 27] The report from AAP's New Challenges in Childhood Immunizations Conference noted that physiological interactions, problems with PCR techniques as well as the potential for contamination could affect PCR study results. Therefore, the report recommends that collaborative studies involving multiple laboratories testing coded, unknown specimens be conducted.[7]

Because measles RNA has been found in multiple organs of people without apparent disease,[7] there is a need to determine

whether the presence of measles vaccine virus is associated with the progression to autism in some children. Intestinal biopsies of children who recently received the MMR vaccine and developed autism need to be compared with intestinal biopsies of children who recently received the MMR vaccine and did not develop autism.[27]

A second mechanistic issue in assessing the biologic plausibility of the hypothesis that MMR vaccination causes autism is to determine how intestinal abnormalities might lead to the developmental disabilities characteristic of autism. Although an association between intestinal and central nervous system abnormalities can be suggested, no clinical or experimental data have demonstrated a causal mechanism. Researchers have suggested that this association could result from the action of a gene or physiologic mechanism related to and simultaneously affecting both systems rather than the result of abnormalities in one system (gastrointestinal system) causing the abnormality in the other (nervous system).[7]

Consideration of alternative explanations?

Although the cause of autism is unknown, many factors have been hypothesized to be associated with some forms of autism. A genetic predisposition to ASD has been suggested from observations that boys are nearly four times more likely to develop the disease than girls[23] and also from studies of siblings and twins. Parents with one child with autism have a 50 times greater risk of subsequent children developing autism than parents without an affected child.[28] Up to 75% of identical (having the same genetic make-up) twins either both have autism or both do not have autism while only 3% of fraternal (do not have the same genetic make-up) twins either both have autism or both do not.[29]

Research suggests that as many as 10 genes could be involved in predisposing children to ASD.[30] In 1995, a working group convened by the National Institutes of Health (NIH) reached a consensus that autism probably results from a genetic susceptibility that involves multiple genes. Studies suggest that the gene HOXA1,[31] inherited metabolic disorders[32] and differences in the major histocompatibility complex (MHC) genes[33, 34] may have supportive roles in susceptibility to autism. Studies conducted in families with more than one member diagnosed with an ASD have also identified possible genetic links to ASD.[30, 35]

Studies have shown that children exposed to thalidomide during the first trimester of pregnancy are at an increased risk for developing autism.[36] One study was able to estimate that the risk period for developing autism following receipt of thalidomide occurs before 24 weeks of pregnancy.[21] Another study found evidence for structural brainstem abnormalities in children with autism which only could have occurred during brainstem development *in utero*.[37]

Children with congenital rubella syndrome (exposure to rubella prenatally)[38-44] and fragile X syndrome[21] are also at increased risk of developing autism.

Although some researchers suggest that the MMR vaccine could serve as a trigger in children already genetically predisposed to autism,[45] other possible environmental, infectious and metabolic triggers have been implicated. An extensive review of the autism literature identified 24 medical disorders possibly related to autism or autistic-like conditions. This review noted that the rate of association of autism with these medical disorders ranged from 11% to 37% in published studies.[46]

Factors other than an actual increase in the number of children with autism may influence the determination of autism prevalence rates. Increased knowledge about autism can lead to better recognition of the disease and the provision of more services for autistic patients. Emerging environmental or lifestyle changes might also affect these numbers. Because the California study that observed a 373% increase in the number of autistic cases in recent years used actual numbers of cases instead of rates,[47] the data are influenced by the steadily increasing California population. In other words, even if the rate of autistic children remains the same over time, a larger number of autistic cases will be found in a larger population than in a smaller one.[45]

Some researchers have hypothesized that autism is a result of abnormal development in the brain and that markers of this abnormal development are present in newborns. These researchers found that in children with autism and in those with mental retardation without autism, blood from the earliest days of life contained concentrations of certain neuropeptides and neurotrophins that differed from those observed in children with cerebral palsy or in normal, control children.[48]

Cessation of exposure?

In the absence of evidence of a causal relationship between MMR and autism, eliminating or modifying the use of MMR vaccine would not be expected to alter the risk of developing ASD. By reducing or eliminating children's exposure to the MMR vaccine, their risk of becoming infected with measles, mumps and/or rubella virus would be expected to increase markedly, resulting in much higher incidences of morbidity and mortality due to these diseases. The measles outbreak of 1989-1991, which occurred because of decreased use of the MMR vaccine during the late 1980s, is a compelling example of the public health impact of reducing vaccine use.[49] During this period, 55,467 cases of measles were reported and there were 136 measles-associated deaths.

Specificity of exposure?

Scientific commentary following the 1998 United Kingdom study[15] has argued that the intestinal syndrome described is not clinically unique and that ileal-lymphoid hyperplasia is non-specific.[16] It is not unusual for young children to have collections of lymphocytes in their intestines. In fact, enlarged collections of lymphocytes in the intestine can occur in up to 25% of healthy children.[27] The authors of the 1998 study contend that although small nodules are considered normal, a more exaggerated change was observed in the patients studied.[50]

Consistency with other knowledge?

Home movies were shown to neurodevelopmental specialists who were blinded to whether the children they were watching eventually were or were not diagnosed with autism. These specialists were able to separate autistic from non-autistic children at one year of age with a high degree of accuracy.[51-55]

Children who were eventually diagnosed with autism have also been predicted from home movies taken at two to three months of age.[56] These studies suggest that the first signs of autism are present earlier than thought and that these symptoms occur prior to the receipt of the MMR vaccine.[21]

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Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD) is a general medical term used to refer to chronic inflammatory diseases of the intestine. IBD can begin at any age, but it usually develops in persons between the ages of 15 and 30 years. IBD is a rare disease with three to 20 new cases reported per 100,000 persons each year in the US. Two common inflammatory bowel diseases are ulcerative colitis and Crohn's disease. These chronic illnesses can inflame the gastrointestinal tract causing bloody diarrhea, abdominal pain and weight loss. Ulcerative colitis can affect the entire large intestine or the rectum. Crohn's disease mainly affects short segments of both the small and large intestine.[1]

An association between measles vaccination and IBD was first proposed in a 1995 cohort study of vaccinated children in the UK who were enrolled in a 1964 trial of a measles vaccine, and followed until 1994. The incidence of IBD in these children was compared to the incidence of IBD in a group of presumably unvaccinated children enrolled in a study of persons born in Great Britain during one week in 1958. Children in the vaccinated cohort had a three-fold increased risk of Crohn's disease and a 2.5-fold increased risk of ulcerative colitis compared with the unvaccinated children.[2]

The validity of this study has been questioned for several reasons. Vaccinated and unvaccinated groups were followed for different periods of time, with follow up of the vaccinated group being approximately half of that for the unvaccinated group.[3] During the study's evaluation of outcome, vaccinated individuals were asked specifically about Crohn's disease and ulcerative colitis, while unvaccinated individuals were asked about "any longstanding illness, disability or infirmity." Moreover, vaccinated and unvaccinated individuals were selected from different populations.[4] Any of these differences in the selection and assessment of vaccinated and unvaccinated study participants could have significantly biased study outcomes.

Temporal relationship?

The incidence of Crohn's disease has increased since the 1940s, but this trend began some 20 years prior to the introduction of the measles vaccine.[5]

A small 1998 study looked at 12 children who were referred to a pediatric gastroenterology unit with histories of normal development followed by loss of acquired skills, diarrhea and abdominal pain. All research subjects except one were diagnosed with ulcerative colitis. In eight of these 12 children, the onset of behavioral symptoms was attributed by the parent or provider to measles, mumps, rubella (MMR) vaccination.[6] However, other investigators suggested that selection bias may have occurred in this study as the report was based on cases referred to a group known to be specifically interested in studying the possible relationship between the MMR vaccine and IBD.[7]

Using data from a Finnish surveillance system created in 1982 when MMR vaccine was first introduced in Finland, comprehensive analysis of 1.8 million individuals and use of almost three million doses of MMR vaccine during a 14-year follow up revealed no cases of IBD.[8]

Strength of association?

A study looking at all individuals born in Great Britain during a single week in 1970 whose vaccination history was accessed from a survey conducted when the children were five years old found no significant association between measles infection at a young age and later development of Crohn's disease or ulcerative colitis. However, the specific combination of measles and mumps infection in the same year of life between birth and age six years was significantly associated with the development of both ulcerative colitis and Crohn's disease later in life.[9]

Dose-response relationship?

The rate of Crohn's disease reported in Finland from 1986 through 1992 was compared to the proportion of the population receiving measles vaccine. While the

GLOSSARY TERMS

Acute
Antigen
Association
Bias
Cases
Chronic
Cohort study
Controls
Crohn's disease
Disease
Enterocolitis
Epidemic
Gastroenterology
Gastrointestinal tract
Ileal lymphonodular hyperplasia
Immune system
Immunization
Immunogold electron microscopy
Incidence
Inflammation
Inflammatory bowel disease
In situ hybridization
In utero
Lesions
Lymphatic tissue
Lymphocytes
Measles
MMR vaccine
Morbidity
Mumps
Peripheral blood mononuclear cells
Polymerase chain reaction
Risk
RNA
Rubella
Selection bias
Systemic
Temporal relationship
Ulcerative colitis
Vaccine
Vaccine Safety Datalink Project
Virus

ACRONYMS

IBD	Inflammatory bowel disease
MCV	Measles-containing vaccines
MMR	Measles, mumps, rubella
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
RNA	Ribonucleic acid

WEB RESOURCES

The American Gastroenterological Association
http://www.gastro.org/public/ibd.html

KidsHealth for Parents
http://kidshealth.org/parent/medical/digestive/ibd.html

National Immunization Program
http://www.cdc.gov/nip/vacsafe/concerns/autism/ibd.htm

proportion of the population receiving at least one dose of measles vaccine increased over this period, the rate of Crohn's disease remained stable among persons from birth to 24 years of age.[10]

Children five to 16 years of age enrolled in a 1994 national measles, mumps, rubella vaccine campaign targeted at school-age children in England were followed for 16 months. Although each of these children were receiving their second dose of MMR vaccine (their first dose was received around the age of one year), researchers found no increase in hospital admissions for Crohn's disease among this group of children.[11]

Replication of findings?

A study utilizing the Vaccine Safety Datalink Project identified 142 persons with IBD born between 1958 and 1989 and compared each of their vaccination records with those of five matched controls. Researchers found that neither administration of MMR vaccine or other measles-containing vaccines (MCV) nor age at vaccination increased the risk of IBD. Rates of IBD were also not elevated in the time immediately following vaccination with either vaccine (MMR or MCV).[3]

A UK study compared 140 individuals with IBD born in or after 1968 with 280 matched controls and found no association between measles vaccination and Crohn's disease, ulcerative colitis or all IBD combined.[12]

Biological plausibility?

In order to prove that the measles vaccine actually causes IBD, it is necessary to prove that the measles virus is definitely present in gastrointestinal lesions, that it is active and that it can cause an inflammatory response. Researchers would also need to determine whether this reaction was caused by the measles virus or by the attenuated (weakened) measles vaccine virus.[1]

Disease occurs when the virus that causes measles disease infects the respiratory system and then spreads to lymphatic tissue, an important part of our immune system. During the acute infection, lymphocytes in the gastrointestinal tract are infected, but whether this causes chronic inflammation is highly questionable. One theory speculates that the measles virus may persist in the intestine in certain individuals and later trigger a chronic inflammatory infection; however, this has not been proven. Because the MMR vaccine contains a very weak live measles virus, it has been suggested that measles vaccine could cause a similar inflammatory process in the intestine. This theory has not been proven and is speculative.

Additional biological evidence that measles infection increases the risk of IBD is based upon laboratory-based investigations looking for evidence of past or persistent measles infection among people with IBD.

Studies have detected measles virus in the intestines of persons with IBD based on *in situ* hybridization techniques[13] and immunogold electron microscopy.[14] Researchers have since argued that these techniques are not sensitive enough to accurately identify measles virus in the bowel,[15] and other researchers using the same laboratory methods could not identify measles virus in the intestines of patients with IBD.[16] Four studies using the more sensitive and specific polymerase chain reaction (PCR) method found no evidence of measles virus ribonucleic acid (RNA) in the gastrointestinal tissues of patients with Crohn's disease or ulcerative colitis.[16-20]

In a study of 20 patients with chronic intestinal inflammation, measles virus RNA was detected in peripheral blood mononuclear cells (PBMC) using the PCR technique. One of eight patients with Crohn's disease and one of three patients with ulcerative colitis were positive. Measles virus RNA was not detected in PBMC from 28 control patients.[21] These findings were considered by the researchers to be indicative of a potential association between MMR vaccine and the IBD of the individual patients. However, vaccination status was given for only one patient and was not given for any of the controls.

Cessation of Exposure?

In the absence of evidence of a causal relationship between the MMR vaccine and inflammatory bowel disease, eliminating or modifying the existing childhood immunization schedule would not be expected to alter the risk of such infections. By reducing or eliminating children's exposure to the MMR vaccine, their risk of becoming infected with measles, mumps and/or rubella viruses would be expected to increase markedly, resulting in much higher incidences of morbidity and mortality due to these diseases. The measles outbreak of 1989-1991, which occurred because of decreased use of the MMR vaccine during the late 1980s is a compelling example of the public health impact of reducing vaccine use.[22] During this period 55,467 cases of measles were reported and there were 136 measles-associated deaths.

Specificity of Association?

In a recent study of 91 patients with a histologically confirmed diagnosis of ileal lymphonodular hyperplasia and enterocolitis, measles virus was detected in the intestinal tissue of 75 using the PCR technique. In comparison, measles virus was only detected in five of 70 control patients.[23] Commentary following the article noted that the technique used could not identify if the whole virus was present or whether the virus was replicating. Researchers also noted the possibility that the measles virus persistence could be the result of the inability of bodies of patients suffering from a developmental disorder that already existed to clear the virus from their intestines.[24] Further, the PCR methods used could not determine if the measles genomic material identified was the result of a case of measles disease, was from a previous injection with MMR vaccine or was from a previous injection with vaccine that contains only measles vaccine virus.[25]

Consideration of alternative explanations?

There are several unproven theories as to the cause(s) of IBD. A possible genetic predisposition has been proposed because IBD is known to occur in the same family.[26] A possible environmental cause has also been suggested because Crohn's disease most often occurs in people who smoke and in residents of Northern European countries and of urban areas. Other theories propose that IBD is triggered by significant emotional events in a person's life, by other infections, or by the body's immune system reacting to unidentified or unknown antigens causing the immune system to respond inappropriately and resulting in chronic inflammation.[1]

Consistency with other knowledge?

Studies have been conducted to examine the development of IBD following *in utero* exposure to measles and measles infection in early life.

In Utero measles exposure:

A Swedish study of 25,000 pregnancies between 1940 and 1949 found that three of the four babies whose mothers experienced a measles infection while she was carrying them had developed Crohn's disease.[27] This rate of disease was much higher than expected. A later study conducted in Denmark followed 25 babies whose mothers had developed measles during pregnancy and found no cases of Crohn's disease.[28] Another study compared 3,076 individuals exposed *in utero* to viral diseases (including measles) to a matched set of unexposed individuals with follow up through ages 16 to 53 years. Among the non-exposed individuals there was one case of ulcerative colitis and one of Crohn's disease, while among those exposed to measles *in utero* there were no cases of IBD.[29] In both of these studies, the rate of IBD was much less than would be expected had the original findings of the Swedish study been replicated.

Postnatal exposure or infection:

The birth records of 257 Swedish individuals with IBD from 1924 through 1957 were compared to 514 matched controls. Individuals with a history of postnatal infections were 5.5 times more likely to develop IBD than individuals without a history of postnatal infection. But the study did not specifically address whether it was measles infection that accounted for the increased risk.[30]

A study in North Carolina compared 322 individuals with IBD to neighborhood controls or acquaintances and found that childhood infections (not just measles infection) increased the risk of Crohn's disease but not of ulcerative colitis. For measles infection specifically, there was an increased risk of Crohn's disease and ulcerative colitis, but in neither case was the risk statistically significant.[31]

The incidence rate of Crohn's disease and ulcerative colitis in persons less than 30 years of age was evaluated in a group of individuals who were born in a three month time period following five different measles epidemics in Sweden. The actual number of cases of Crohn's disease in this group was 1.46 times higher than the expected number of cases (57 cases were reported compared to the expected number of 39 cases). The number of ulcerative colitis cases in this group was not significantly different from the expected number of cases.[32] A study in the UK that analyzed patients with Crohn's disease diagnosed between 1972 and 1989 found no increased risk for Crohn's disease among children born in years with high measles incidence rates compared with children born in other years.[33]

In the 1970 British Cohort Study, measles infection at 10 years of age or younger was not associated with an increased risk for Crohn's disease or ulcerative colitis by age 26. However, the rare combination of mumps and measles infection in the same year of life was associated with a statistically significant increase of both Crohn's disease and ulcerative colitis.[11]

A Mayo Clinic study followed 662 patients with measles prior to age five during the period from 1950 to 1966 for 10 to 48 years. The number of individuals observed to have Crohn's disease or ulcerative colitis were compared with the number expected based on age and gender-specific population incidence rates. A total of six individuals with Crohn's disease and six with ulcerative colitis were found (compared with 1.9 and 2.0 expected cases, respectively.).[34]

In a study looking at two UK birth cohorts, 26 patients with Crohn's disease and 29 patients with ulcerative colitis were identified. Neither measles nor mumps infection by seven years of age were associated with an increased risk for Crohn's disease or for ulcerative colitis.[35]

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Multiple Immunizations

Currently, there are 11 licensed vaccines in the US that are recommended for universal use by children during the first two years of life.[1,2] These vaccines are administered through as many as 20 separate inoculations. The personal and the public health benefits of these immunizations are extremely important, but the use of syringes and needles to administer vaccines is often frightening and uncomfortable to children, and distressing to parents.[3] Because of the large number of immunizations given to children prior to school entry, particularly those administered during the first two years of life, some parents and others question whether children receive too many immunizations. A national telephone survey in 1999 of parents of children six years of age and younger and expectant parents revealed that 23% questioned the number of immunizations recommended for children and 25% worried that the vaccines might weaken the immune system.[4]

Concerns about the number of immunizations recommended for children and the development of the immune system focus on three issues: (1) the number of inoculations given; (2) the total number of antigens introduced by the immunizations; and (3) whether multiple immunizations might adversely affect the development of the child's immune system. Although the first two concerns were addressed in the section *Vaccines and How They Work*, the third concern, the potential for multiple immunizations to cause abnormal development of the immune system, warrants further consideration.

Some have postulated that the introduction of 123-126 antigens during the first two years of life might result in overstimulation of the immune system potentially leading to abnormal development of the immune system.[2,4-6] The postulated abnormal development might then result in an increased likelihood that the child will be more susceptible to other infectious agents, or to the development of allergies or autoimmune diseases,[5] which are considered indicators of immune system dysfunction. Numerous reports have suggested that as personal and community hygiene has improved in developed countries, the number and types of antigens to which young children are exposed has changed. [5,7-9] The notion that immune system dysfunction might be related to changes in antigen exposure during immune system development is known as the hygiene hypothesis.

As noted in *Vaccines and How They Work*, exposure of the developing immune system to many different bacterial, viral and other antigens is responsible for the development and maturation of B and T cells.[10,11] As currently conceived, postnatal exposure to such agents promotes the development of a subset of helper T cells called Th1 cells.[10] Antigen activated Th1 cells release various cytokines that regulate the normal immune response to viruses, bacteria and other antigens.[10] When a second subset of helper T cells, Th2 cells, are stimulated by antigens, they release certain cytokines that induce B cells to produce a particular type of antibody molecule (termed IgE) that can trigger allergic reactions as well as promoting the development of blood cells called eosinophils that contribute to allergic reactions.[10,11] The hygiene hypothesis suggests that when exposure to various bacteria, viruses and other antigens during postnatal maturation of the immune system is reduced, as might result from increased hygienic practices, the immune system develops a bias toward eliciting Th2-mediated responses to certain antigens.

Reduced exposure to bacterial, viral and other relevant antigens may also influence the development of the immune system by altering the production of a cytokine known as IL-10, which plays a pivotal role in regulating a variety of components of the immune response.[12,14,15] Typical exposure to such antigens in the absence of enhanced hygienic conditions results in the production of IL-10, which limits the ability to develop allergic and autoimmune responses.[8] Under conditions of enhanced hygiene where sustained exposure of the developing immune system to diverse antigens is reduced, production of IL-10 may be reduced. This, in turn, may limit the ability of this cytokine to suppress the activity of cells involved in allergic and autoimmune reactions, thus disposing the person to the develop allergies or autoimmune diseases.[5,8]

GLOSSARY TERMS

Adjuvant
Allergy
Antibody
Antigen
Association
Asthma
Autoimmune disease
B cell
Bacteria
Bias
Bystander activation
Cases
Cell-mediated response
Chronic
Congenital rubella syndrome
Coxsackievirus
Cytokines
Cytomegalovirus
Diabetes
Disease
Dose response relationship
Dysfunction
Eosinophil
Group A streptococcus
Hay fever
Helper T cell
Heterologous infections
Hygiene hypothesis
IgE
IL-4
IL-10
Immune response
Immune system
Immunization
Incidence
Inflammation
Institute of Medicine
Measles
MMR vaccine
Molecular mimicry
Morbidity
Multiple sclerosis
Myelin
Pancreas
Pathogens
Protein
Rheumatic fever
Rheumatic heart disease
Risk
Rubella
Superantigens
T cell
Temporal relationship
Th1 cell
Th2 cell
Thrombocytopenia
Type 1 diabetes
Vaccine
Virus

ACRONYMS

CDC	Centers for Disease Control and Prevention
IgE	Immunoglobulin E
IL-4	Interleukin 4
IL-10	Interleukin 10
IOM	Institute of Medicine
MHC	Major histocompatibility complex
MMR	Measles, mumps, rubella

WEB RESOURCES

American Diabetes Association
http://www.diabetes.org/main/community/info_news/news/vaccines.jsp

Asthma and Allergy Foundation of America
http://www.aafa.org

Institute of Medicine
http://www.iom.edu/iom/iomhome.nsf/pages/multiple+immunizations

Multiple Sclerosis Foundation
http://www.msfacts.org

National Immunization Program
http://www.cdc.gov/nip/vacsafe/concerns/gen/multiplevac.htm

National Institute for Health
http://www.nih.gov/hi/topics/autoimmune/autoimmunity.htm

National Multiple Sclerosis Society
http://www.nmss.org

The Institute of Medicine (IOM) Immunization Safety Review Committee recently examined the scientific evidence surrounding whether multiple immunizations were associated with various types of immune dysfunction that might result from impaired immune system development. The committee found no epidemiological evidence supporting a causal relationship between multiple immunizations and an increase in the incidence of infections by other pathogens or an increase in the likelihood of developing type 1 diabetes, an autoimmune disease associated with immune dysfunction. There was insufficient information available to assess whether multiple immunizations might increase the risk of allergic disease. The committee found only a theoretical link between multiple immunizations and the development of either autoimmune or allergic disease based on current understanding of the biological mechanisms associated with each.[5]

The following more closely examines the work of the IOM committee and others in examining the relationship between multiple immunizations and immune system dysfunction relative to susceptibility to other infections and to the development of allergies or autoimmune diseases.

Susceptibility to Other Infections

The idea that administration of multiple immunizations could lead to a child becoming more susceptible to other infections reflects the notion that if the immune system is busy responding to vaccine-associated antigens, its ability to respond to real infections may be impaired. Infections due to agents other than those targeted by vaccines are referred to as heterologous infections in the IOM report.[5]

Temporal relationship?

In order to determine whether use of increasing numbers of immunizations has led to increased susceptibility to other infections, rates of infections in children would need to be compared to the number of immunizations given over time. If the rate of childhood infections increased as the number of vaccines doses given increased, a temporal relationship could be established. However, no such studies have been conducted. In lieu of such studies, a number of investigators have examined morbidity and mortality data among immunized children in the US and abroad using various study designs. The seven studies reviewed by the IOM committee failed individually as well as collectively to demonstrate a causal relationship between immunization and susceptibility to heterologous infections.[5] None of the studies specifically attempted to determine the relationship between multiple immunizations and the risk of developing such infections.

Strength of association?

A strong association between the receipt of multiple immunizations and increased susceptibility to other infections would mean that those children receiving the fewest immunizations would acquire the fewest heterologous infections, while those receiving the greatest number of immunizations would experience the greatest number of such infections. Again, the studies reviewed by the IOM committee were not specifically designed to assess the role of multiple immunizations. Within the context of the designs used, there was no evidence that immunization increased the risk of heterologous infections.[5]

Dose-response relationship?

One approach to assessing the risk of heterologous infection would necessitate placing different cohorts of children on different immunization schedules so that the members of each cohort received a different number of immunizations. The children would be monitored for a biologically relevant period of time, and all infections recorded and the causative agent(s) determined. If there was a statistical association between increasing numbers of immunizations and increasing incidence of infection, the study would provide scientific evidence of a temporal relationship. Such studies have not been conducted and would be lengthy and costly, and the ethical basis for such studies would be subject to question.

In lieu of such studies, a number of investigators have examined morbidity and mortality data among immunized children in the US and abroad using various study designs. The seven studies reviewed by the IOM committee failed individually as well as collectively to demonstrate a causal relationship between immunization and susceptibility to heterologous infections.[5] None of the studies examined by the IOM committee[5] were specifically designed to determine if increasing the number of immunizations increased susceptibility to heterologous infection.

Replication of findings?

There are no published studies demonstrating a relationship or absence of a relationship between multiple immunizations and susceptibility to heterologous infections. The results of the seven studies reviewed by the IOM committee were highly variable, and flaws in the design of these studies further limited assessment of the reproducibility of the findings.[5]

Biologic plausibility?

Laboratory research has shown that when multiple antigens are given at one time, the strength, type and effectiveness of the immune response to each will differ in comparison to the response observed when each is given separately.[12,13] A variety of mechanisms, such as suppression of the ability of the immune system to respond to certain antigens, ineffective presentation of certain antigens or the overwhelming of the immune system,[10,11] have been suggested to explain such observations. Although none of these mechanisms have been shown to apply to the multiple immunizations given to children, the IOM committee concluded that such mechanisms could, in theory, influence the susceptibility to heterologous infections of children receiving multiple immunizations.[5]

Consideration of alternative explanations?

Susceptibility to infectious diseases is influenced by many factors, including exposure, dose, immune status, personal hygiene, patterns of gene expression and others.[13,14] Any or all of these factors could influence whether a person receiving multiple immunizations would be at increased risk for developing heterologous infections. Thus, there are many alternative explanations that might account for susceptibility to such infections, and only careful, well-defined scientific studies would be able to determine the role of each.

Cessation of exposure?

In the absence of evidence of a causal relationship between multiple immunizations and susceptibility to heterologous infections, eliminating or modifying the existing childhood immunization schedule would not be expected to alter the risk of such infections. By reducing or eliminating children's exposure to multiple immunizations, their risk of becoming infected by pathogens responsible for vaccine-preventable diseases would be expected to increase markedly, resulting in much higher incidences of morbidity and mortality due to these diseases. The measles outbreak of 1989-1991, which occurred because of decreased use of the MMR vaccine during the late 1980s is a compelling example of the public health impact of reducing vaccine use.[15] During this period 55,467 cases of measles were reported and there were 136 measles-associated deaths.

Consistency with other knowledge?

If exposure to multiple immunizations was specifically associated with increased susceptibility to heterologous infections, one would expect that as children progress through the recommended schedule of immunizations there would be an increase in the number of cases of infectious diseases reported, particularly those that are not vaccine preventable. Infectious disease statistics available from the Centers for Disease Control and Prevention (CDC)[16] do not suggest that the incidence of infectious diseases increases with age over the first six years of life.

Immunizations have been used effectively to prevent infectious diseases in the US for nearly 200 years. The use of vaccines has accelerated in recent years resulting in both an increase in the number of diseases that can be prevented by vaccination and in an increase in the number of immunizations given. Throughout this period, the incidence of both vaccine-preventable diseases as well as other infectious diseases has declined.[16] At this time there is no scientific evidence that multiple immunizations increase the risk of heterologous infections.

Susceptibility to Allergic Reactions

Speculation that multiple immunizations might be associated with allergic disease reflect the increasing incidence of asthma and some allergies in the US and in other countries over the past 40 years.[7,8] The hygiene hypothesis offers a biologically-based, but unproven, explanation for the increased incidence of allergic disease. Although this trend began many years before the inception of the current vaccination schedule for children, some have suggested that multiple immunizations of children whose immune systems are theoretically predisposed to Th2 responses may trigger allergic reactions.

The IOM committee focused on epidemiologic studies of hay fever and asthma in evaluating the relationship between multiple immunizations and the development of allergic disease. Generally, more information is available about these two diseases than is available about other allergic diseases. The committee noted that the six germane studies suffered from a variety of design and methodological flaws, and therefore concluded that the available data were insufficient to determine whether there was a causal relationship between multiple immunization and the incidence of hay fever and asthma.[5] As mentioned above in the discussion of susceptibility to heterologous infections, designing and conducting an appropriate study for assessing causality would pose a considerable challenge.

Temporal relationships?

Allergic disease may become apparent at different ages in different people.[17] Food allergies and asthma are often diagnosed in children less than three years of age, although many outgrow the symptoms.[17] For example, the incidence of asthma among children less than one year old was three to four times greater than the incidence among children one to four years of age.[18] Hay fever may not be diagnosed until the person is an adolescent or adult. It is unclear whether the appearance of allergic disease is temporally associated with the age range during which most childhood immunizations are given.

Strength of association?

In the absence of information supporting or refuting an association between multiple immunizations and allergic disease, as represented by the IOM committee's consideration of hay fever and asthma,[5] it is not feasible to assess the strength of the association. A strong association between the receipt of multiple immunizations and increased susceptibility to asthma and hay fever likely would mean that the incidence of these diseases would be lowest among children receiving the fewest immunizations, and greatest among those receiving the greatest number of immunizations.

Dose-response relationship?

In evaluating the relationship between multiple immunizations and allergic disease, one would expect a lower incidence of disease among those given low doses (few immunizations) and a greater incidence of allergic disease among those given high doses (more immunizations). The dearth of relevant data[5] precludes assessing whether a dose-response relationship exists in this case.

Replication of findings?

The IOM committee report[5] did not identify any studies demonstrating a relationship or absence of a relationship between multiple immunizations and susceptibility to developing hay fever or asthma.

Biologic plausibility?

Allergic reactions are typically Th2 cell-mediated and result from IgE antibodies directed against antigens associated with insects, toxins, pollen and other materials in the environment.[19] Much of the asthma reported among children in impoverished urban areas is attributed to allergens associated with cockroaches.[20] Although progress has been made in understanding allergic reactions, the factors responsible for initiating a Th2/IgE response remain incompletely understood.

A variety of experimental data support the hygiene hypothesis, yet it remains a theoretical concept.[5,8,9] If improved personal and community hygiene alters antigen exposure during the development the immune system and leads to abnormal regulation of the immune response, then the response could be skewed in the direction of allergic responses.[5] The IOM committee concluded

that too little is known about the mechanisms that might link the hygiene hypothesis, multiple immunizations and risk of developing allergy to consider such a linkage to be more than a theoretical possibility.[5]

The IOM committee[5] noted that a number of the recommended vaccines include alum as an adjuvant, i.e., a substance that is incorporated into a vaccine to enhance the immune response to the vaccine without eliciting an immune response to itself.[10,11] The adjuvant effect of alum is apparently related to its ability to induce the production of the cytokine IL-4 by certain immunologically active cells, which in turn promotes Th2 cell-mediated responses.[5] Because a number of vaccines given to children contain alum, the IOM committee concluded that there is a theoretical possibility that multiple immunizations could predispose the immune system to eliciting Th2 responses.[5] The committee was unable to assess whether this theoretical possibility might increase the risk of developing hay fever or asthma.

Consideration of alternative explanations?

The increase in the incidence of allergic disease observed over the past four decades coincides with a period of profound changes in American lifestyles, some of which may be reflected in the hygiene hypothesis. The changes in the incidence of allergic disease and lifestyle changes both pre-date the period during which the number of immunizations given to children increased. The likelihood that a person will develop an allergic disease is influenced by a variety of factors, including exposure to allergens and genetic predisposition.[21] For example, children of parents who have allergies are more likely to have allergic reactions than children of parents who do not have allergies.[21] The genetic factors responsible for such associations have yet to be determined. Similarly, no data are available to assess whether and how these genes might influence the responses to multiple vaccines.

Cessation of exposure?

In the absence of evidence of a causal relationship between multiple immunizations and susceptibility to developing allergic disease, the risks of developing allergic disease are unlikely to be altered by eliminating or modifying the existing childhood immunization schedule. As noted in the section on heterologous infection, reducing or eliminating the immunization of children would result in outbreaks of vaccine-preventable diseases.

Specificity of association?

If exposure to multiple immunizations was specifically associated with increased risk of developing allergic disease, one would expect that as children progress through the recommended schedule of immunizations there would be an increase in the number of cases of allergic disease. Although Th2 responses are known to contribute to allergic diseases, Th2 responses also are observed among people infected with parasitic worms.[5] Such infections are relatively common in many developing countries were the incidence of asthma and allergy are low. Hence, the hygiene hypothesis cannot fully account for the observed patterns of allergic disease.

Consistency with other knowledge?

Immunizations have been used effectively to prevent infectious diseases in the US for nearly 200 years. The use of vaccines has accelerated in recent years resulting in both an increase in the number of diseases that can be prevented by vaccination and in an increase in the number of immunizations given. Throughout this period, the incidence of both vaccine-preventable diseases as well as other infectious diseases has declined.[15] At this time, there is no scientific evidence that multiple immunizations increase the risk of developing allergic disease.

Susceptibility to Autoimmune Disease

Over the past several decades, the incidence of autoimmune diseases like type 1 diabetes and multiple sclerosis, have increased.[5] Autoimmune disease occurs when the immune system produces immune effectors that directly damage the person's own cells, tissues and organs. Autoimmune diseases may be systemic, where the symptoms are manifest in a variety of tissues and organs such as multiple sclerosis, or they may be organ-specific, such as type 1 diabetes which effects the pancreas.[22] Although some autoimmune diseases may be diagnosed during childhood, most do not become apparent until the second, third or even fourth decade of life. In general, autoimmune diseases are more commonly diagnosed in females than males,[22] although the reasons for this disparity have yet to be determined.

The normal immune system includes both B and T cells that possess cell surface receptors capable of recognizing and binding to self antigens, i.e., molecules that are normally present in the tissues and organs of the body. A variety of mechanisms have been postulated to account for the immunological tolerance to self antigens that prevent the activation of these cells.[22,23] Even so, normal individuals typically sustain some modest degree of ongoing self-reactivity.[22,23] When the mechanisms that hold these autoimmune effectors in check are compromised, autoimmune disease results.[22,23]

The IOM committee focused on epidemiologic studies of type 1 diabetes in evaluating the relationship between multiple immunizations and the development of autoimmune disease. Generally, more is known about type 1 diabetes than is known about other autoimmune diseases. The committee noted that although the eight relevant studies differed in design, there was no evidence of a causal relationship between multiple immunizations and type 1 diabetes.[5]

Temporal association?

The natural history of most autoimmune diseases is characterized by late onset, diversity of affected target organs, a preponderance of cases among females and other unique features. These disease characteristics suggest that there is no temporal relationship between the receipt of multiple immunizations during the first six years of life and the onset of autoimmune disease.[22,23]

Strength of association?

In the absence of an association between multiple immunizations and autoimmune disease as exemplified by type 1 diabetes,[5]

it is not possible to evaluate the strength of the association. A strong association between the receipt of multiple immunizations and risk of developing type 1 diabetes likely would be manifest by a pattern in which the incidence of this disease would be lowest among children receiving the fewest immunizations, while the incidence would greatest among those receiving the greatest number of immunizations.

Dose-response relationship?

If exposure to multiple immunizations was specifically associated with increased risk of developing autoimmune disease, one would expect that as children progress through the recommended schedule of immunizations there would be an increase in the number of cases of this disease. Although the number of reported cases of autoimmune disease in the US are not well characterized, at least in the case of type 1 diabetes, the incidence seems to be increasing.[5] Evidence from several studies has failed to demonstrate a relationship between immunization and type 1 diabetes,[5] although none of the studies specifically addressed disease incidence relative to the number of immunizations given.

Replication of findings?

The IOM committee report[5] did not identify any studies demonstrating or refuting a relationship between multiple immunizations and susceptibility to developing type 1 diabetes. Because most existing studies of the potential relationships between vaccination and autoimmune disease generally consider single vaccine series, there are little or no data addressing possible relationships between multiple immunizations and autoimmune disease.

Biologic plausibility?

Autoimmunity is an incompletely understood phenomenon that has been associated with a variety of biological mechanisms.[22,23] These include a skewing of the immune response from one directed against a foreign antigen to one that is directed against a biochemically similar self antigen. In this case, the foreign antigen is said to mimic the self antigen, i.e., molecular mimicry. It has been suggested that autoimmunity may result when inappropriate presentation of self antigens occur, resulting in a strong immune responses, or when there is breakdown of regulatory mechanisms that ordinarily limit the ability of the immune system to respond to self antigens or that lead to inappropriate recognition of self antigens.[22,23] Inflammation at sites of infection could contribute to the induction of such mechanisms.[31] It is unclear whether any of these possible mechanisms are activated as a result of receiving multiple immunizations.

The IOM committee report[5] concluded that molecular mimicry could potentially be a factor in the induction of type 1 diabetes. The concept of molecular mimicry as it applies to the immune response suggests that some foreign antigens may be sufficiently similar in structure to certain self antigens such that the immune response directed against the foreign antigen might cross react with the self antigen.[22,23,25] This, in turn, could lead to production of a self-reactive immune response that gives rise to chronic or recurrent autoimmune disease.

A classic example of molecular mimicry is autoimmune-mediated rheumatic fever that occurs in some people as a consequence of Group A streptococcal infections. In this case, antibodies against the bacterial antigens bind to structurally similar proteins found in the heart.[26] These localized antibody/self antigen interactions contribute to the onset of rheumatic heart disease. Infections by coxsackievirus, cytomegalovirus, and rubella virus have been associated with type 1 diabetes.[27] This evidence along with the association of congenital rubella syndrome with type 1 diabetes led the IOM committee to conclude that molecular mimicry could constitute a linkage between immunization and autoimmune disease, although the role of multiple immunizations in such a relationship remains to be determined.[5]

It also has been proposed that infectious agents may induce the activation of an autoimmune response by acting as superantigens or through bystander activation.[24,28] T cells typically are activated when a receptor on the cell surface specifically recognizes and binds to an antigen that is presented by an appropriate MHC molecule (see *Vaccines and How They Work*). Superantigens are antigens that stimulate T cells by direct interaction between the antigen and the receptor molecule independent of the receptor's antigen binding site. The former might be envisioned as inserting a key into a lock in a door handle to open a door, while superantigen activation might be seen as touching the key to the surface of the handle to open the door. Superantigens stimulate T cells independently of the specificity of the cell. Thus, antigens from invading bacteria or viruses could activate T cells that recognize self antigens.[24] Once activated these cells could trigger chronic or episodic autoimmune disease.

As described in *Vaccines and How They Work*, large numbers of inflammatory cells are recruited to a site of infection. T cells activated by antigens as well as other cells at the infection site release a complex mix of cytokines and other regulatory molecules into the local environment. Hence, immune cells present at the site, but not specifically participating in the response, may become activated by virtue of being present when and where these molecules are released.[24] Some of these activated bystander cells may trigger the onset of autoimmune disease. The cytokine-rich environment also could induce antigen presenting cells to inappropriately present self antigens, again setting the stage for the development of autoimmune disease.[24] Processes such as these that alter regulation of the immune response lend support to the hygiene hypothesis as it applies to autoimmune disease.[8]

Scientific evidence exists for the various mechanisms outlined above that might link infections with the risk of developing autoimmune disease.[22,23,24] Other research suggests that susceptibility to developing autoimmune disease is influenced by a variety of other factors, including genetic background.[29,30,31] Whether and how the various mechanisms that have been proposed to explain these relationships apply to vaccines remains unclear. A recent review suggests that in most cases there are few data implicating vaccines in the induction of autoimmune disease.[29] One possible exception is an apparent increase in the risk of developing thrombocytopenia, an autoimmune-mediated blood disorder, after MMR immunization. However, this risk is small relative to the risk of developing one or more of these infections in the absence of immunization.[29] Most existing studies of the

potential relationship between vaccination and autoimmune disease generally consider single vaccine series, and have not specifically addressed possible relationships between multiple immunizations and autoimmune disease.

Consideration of alternative explanations?

In addition to exposure to infectious agents, genetic and environmental factors have been associated with the development of autoimmune diseases.[22,23,29-31] In the absence of definitive evidence linking multiple immunizations to the development of autoimmune disease, these other factors need to be considered in any attempt to explain how multiple immunizations might be causally related to autoimmune disease.

Cessation of exposure?

In the absence of evidence of a causal relationship between multiple immunizations and susceptibility to developing an autoimmune disease, the risks of developing such diseases are unlikely to be altered by eliminating or modifying the existing childhood immunization schedule. As noted in the section on heterologous infection, reducing or eliminating the immunization of children would result in outbreaks of vaccine-preventable diseases.

Specificity of association?

If exposure to multiple immunizations was specifically associated with increased risk of developing autoimmune disease, one would expect that as children progress through the recommended schedule of immunizations there would be an increase in the number of cases of such disease. Although the number of reported cases of autoimmune disease in the US are not well characterized, at least in the case of type 1 diabetes the incidence seems to be increasing.[5] Evidence from several studies has failed to demonstrate a relationship between immunization and type 1 diabetes,[29] although none of the studies specifically addressed disease incidence relative to the number of immunizations given.

Consistency with other knowledge?

At this time there is no scientific evidence that multiple immunizations increase the risk of developing autoimmune disease.

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Bovine Spongiform Encephalopathy (BSE)

Bovine spongiform encephalopathy (BSE) is an incompletely understood infectious disease of cattle. First described in the United Kingdom in 1986, this neurodegenerative disease of the brain results in apprehension, loss of orientation and locomotor disturbances that can lead to frenzied behavior.[1] Hence, the name "mad cow disease." The brain tissue of affected cows is characterized by cell damage and loss, and by the formation of vacuoles, small clear areas within the brain tissue that give it a sponge-like (spongiform) appearance.[2]

Prior to 1986, cattle were not known to develop spongiform encephalopathies. However, this type of disease has been observed in sheep for over 200 years. This disease, known as scrapie, is particularly common in the United Kingdom. Although cattle and sheep have historically co-existed on farms, no prior evidence existed of direct sheep to cow transmission of scrapie, nor did evidence that scrapie could be transmitted to humans. Spongiform encephalopathies were known to affect a variety of animals, and each was considered to be species-specific.[2]

For many years, European farmers fed cattle high protein supplements prepared from livestock carcasses, including those of sheep, which were boiled and treated with organic solvents to produce meat and bone meals.[1, 2] During the early 1980s, these rendering practices were changed to reduce reliance on solvents. Although not previously known to infect cattle, these changes are believed to have facilitated the transmission of the scrapie agent to cattle via the feed supplements.[1, 3]

The causative agent for scrapie and the other spongiform encephalopathies was first described in 1982 as an atypical form of a protein (referred to as a prion) normally found in the brain.[4] A variety of studies give credence to the prion hypothesis, yet other hypotheses have been advanced, suggesting that a virus or virino may be the infectious agent.[2,5]

Creutzfeldt-Jakob disease (CJD) and kuru are prion-associated spongiform encephalopathies that occur in humans. Symptoms of these diseases typically progress from memory loss and confusion, to behavioral and locomotor abnormalities, to a host of neurological problems.[3] In the case of CJD, which occurs at a rate of less than one per million worldwide, the disease progresses extremely rapidly. The interval between diagnosis and death is typically four months.[3] The etiology and epidemiology of CJD are not well characterized, but the disease tends to be diagnosed in people 50 years of age and older. Kuru is the prototypical human prion disease and has been reported only among members of a small population native to Papua New Guinea.[6] This population is unique in that during the mid-20th century, funeral practices included ritual consumption of brain tissue from the deceased.[6] Those persons engaging in such practices, regardless of age, were at risk of developing kuru. This disease occurred among individuals representing a wide range of ages. The interval between initial exposure to the kuru prion and the onset of disease was as much as 30 years. Since then, kuru has been largely eradicated through the cessation of such practices.[7] There is no known treatment for any of the prion-associated diseases.[3]

Soon after the diagnosis of the first case of BSE in the UK in 1986, public health professionals expressed concern that humans exposed to BSE-tainted beef products may be at increased risk for developing BSE- or CJD-like disease.[2, 3, 8] Efforts were initiated to eliminate the disease by culling cattle exhibiting BSE symptoms and, ultimately, banning all animal-derived feed supplements. Over 4.5 million asymptomatic cattle also were destroyed on the presumption of possible exposure to the BSE prion.[8]

A public health surveillance program was initiated in the United Kingdom in 1990 and by early 1996 10 cases of CJD-like disease were attributed to exposure to the BSE prion.[1, 8] Because each affected person was less than 45 years of age and, on autopsy, was found to share a unique type of spongiform change in the brain, the disease was designated new variant CJD or nvCJD, later shortened to vCJD. Symptoms of vCJD include psychiatric and sensory changes and altered electroencephalographic

GLOSSARY TERMS

Association
Bovine spongiform encephalopathy
Case ascertainment
Cases
Creutzfeldt-Jakob disease
Disease
Dose-response relationship
Electroencephalographic
Encephalopathy
Epidemiology
Etiology
Immunization
Kuru
Neurodegenerative disease
Phase I study
Prion
Protein
Rendering
Risk
Scrapie
Serum
Solvents
Spongiform encephalopathies
Temporal relationship
Vaccine
Virino
Virus

ACRONYMS

BSE	Bovine spongiform encephalopathy
CJD	Creutzfeldt-Jakob disease
CBER	Center for Biologics Evaluation and Research (FDA)
FDA	Food and Drug Administration
nvCJD	New variant Creutzfeldt-Jacob disease
vCJD	Variant Creutzfeldt-Jacob disease

WEB RESOURCES

National Partnership for Immunization
http://www.partnersforimmunization.org/what.html

Public Health Service Recommendations
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4950a4.htm

National Immunization Program
http://www.cdc.gov/nip/vacsafe/concerns/bse/default.htm

Food and Drug Administration
http://www.fda.gov/cber/bse/bse.htm

National Network for Immunization Information
http://www.immunizationinfo.org/healthprofessionals/index.cfm

patterns; the average duration of symptoms was 14 months.[3] Through early February 2001, 98 confirmed or probable cases of vCJD had been reported; 94 cases were in the United Kingdom, three in France and one in Ireland.[9]

These cases are presumed to have resulted from dietary exposure to meat or meat products derived from BSE-afflicted cattle.[1-3, 8] However, little information is available regarding their level of exposure, i.e., how much beef they ate, the types of products, how they were prepared, etc. An investigation of a cluster of five cases of vCJD within a small area in central England where a limited number of cattle producers supply the area's beef, implicated specific butchering practices that led to contamination of meat by brain tissue from affected animals.[10]

In 1997, the death of a young woman with vCJD raised further questions about the dose, incubation period and medium of exposure because of her 10-year history as a vegetarian.[11] Because of her abstinence from beef, the possibility was raised that the BSE prion may have been transmitted via dairy products or through cosmetics or pharmaceutical products that contain gelatins or other materials derived from cattle. Ten years of intense vCJD case ascertainment practices in the United Kingdom has not revealed any such associations.

Cattle-derived products, e.g., blood, serum, purified proteins (enzymes, etc.), gelatins and extracts, may be used in the production of vaccines. Several independent panels of scientists have evaluated the possibility that the BSE prion might be transmitted to humans via a vaccine. The US Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) convened a joint meeting of the Transmissible Spongiform Encephalopathy Committee and the Vaccines and Related Biological Products Advisory Committee during 2000. They concluded that there was no evidence that vCJD has occurred in the US and that there is no evidence that any vaccines are contaminated with the BSE prion. Indeed, the probability of any such contamination is remote, i.e., on the order of one in two billion doses for a bacterial toxoid vaccine or one in 40 billion doses for a vial vaccine.[12] A current list of vaccines using bovine-derived materials from countries on the US Department of Agriculture BSE list or from countries in which the status of BSE is unknown can be found at www.fda.gov/cber/bse/bse.htm#usda. There is no evidence that vCJD has been transmitted to people by vaccination.[13] A review of 52 of the vCJD cases reported in the UK found no evidence of an association between vaccination and vCJD disease.[14]

In the interest of assuring public confidence in the safety of vaccines, given their public health value, the US Public Health Service subsequently recommended that all vaccine manufacturers obtain cattle-derived materials used in vaccine production only from countries where there is no known risk of BSE.[15]

Temporal relationship?

Although the available data suggest a temporal relationship between dietary exposure to BSE and the onset of vCJD, the absence of any association between vaccination and vCJD negates a temporal association between the two.

Strength of association?

The small number of cases of vCJD reported to date in the UK relative to the numbers of people presumably eating beef and beef products during the early and mid 1980s suggest that factors other than beef consumption alone influence BSE transmission and/or disease onset. Indeed, evidence does suggest that people expressing a particular gene may be susceptible to developing vCJD under appropriate, but ill-defined, exposure to the relevant prion.[16] Hence, the association between dietary exposure and disease is not strong. In the absence of any association between vaccination and vCJD, the strength of an association cannot be assessed.

Dose-response relationship?

A dose response relationship has not been established relative to dietary exposure to BSE-tainted meat and meat products. Because no alternative routes of exposure, e.g., vaccination, have been identified, it is impossible to collect meaningful dose response data with respect to other routes of exposure.

Replication of findings?

In the absence of evidence of a causal relationship between vCJD and vaccination, there are no studies to be replicated.

Biologic plausibility?

Although the data support the biologic plausibility of BSE prion transmission to humans via contaminated meat and meat products, and the subsequent development of vCJD, the biologic plausibility that the disease agent can be transmitted with vaccines is considered remote and hypothetical.

Consideration of alternative explanations?

An atypical protein or prion has been identified as the agent responsible for BSE, and a variant of that agent is considered to be responsible for causing vCJD. Some investigators consider the prion to be a marker for a virus or virino that may be the disease-eliciting agent. Such distinctions have limited relevance to the vaccine issue given the absence of an association between immunization and vCJD.

Cessation of exposure?

Steps taken in the United Kingdom subsequent to the identification of BSE and its potential association with vCJD resulted in the virtual elimination of BSE from food animals. Thus, humans are no longer exposed to BSE-tainted meats and meat products. This is expected to result in decreasing numbers of case reports, although the prolonged (and undefined) incubation period and duration suggest that the number of cases reported annually may continue to increase for some period of time.[17,18] Because vaccines are not known to be contaminated with the BSE prion, halting exposure to vaccines would serve no purpose relative to vCJD but would significantly compromise the public's protection against serious infectious diseases.

Specificity of the association?

The association between dietary exposure to BSE-tainted meats and meat products and vCJD is weak given the inability to link cases to specific exposures. In the absence of evidence suggesting an association between vaccines and vCJD, there are no grounds for trying to ascertain specificity of association.

Consistency with other knowledge?

That the occurrence of vCJD is limited to Western Europe, that it is not associated with vaccination, and that there is no evidence to suggest that vaccines in use elsewhere are associated with vCJD, indicates a consistency of knowledge that excludes vaccines from consideration as a possible source of vCJD.

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Thimerosal

Thimerosal is a preservative that has been used in some vaccines and other products since the 1930s as a safeguard against contamination after multi-dose vaccine vials are opened. Disease outbreaks have occurred following contamination of multi-dose vaccine vials in the US and other countries. For example, in April 1995, three infants died in India from toxic shock syndrome after they received contaminated measles vaccine at one health center. While use of thimerosal as a preservative does not eliminate the possibility of bacterial contamination, it can greatly reduce its likelihood. The vaccines used in the US that can contain thimerosal as a preservative include diphtheria, tetanus, acellular pertussis (DTaP), *Haemophilus influenzae* type b (Hib), hepatitis B, influenza, rabies, varicella and pneumococcal polysaccharide.[1] However, all vaccines on the currently recommended childhood immunization schedule for children age six years or younger are available without thimerosal in the US.[3]

According to the Food and Drug Administration (FDA) Modernization Act of 1997, the FDA is required to review and assess the risk of all mercury-containing foods and drugs. Because ethyl mercury is contained in thimerosal, US vaccine manufacturers were requested under this Act to provide more detailed information about the thimerosal content of their vaccines that contain this compound as a preservative.[1, 2] In 1999, FDA review of this information suggested that some infants who have received all of their recommended vaccines may be exposed to levels of ethyl mercury in vaccines that could exceed the Environmental Protection Agency (EPA) guidelines established for the intake of methyl mercury, a related compound known to be associated with adverse health effects.

Vaccine surveillance systems have revealed that other than local, mild vaccine reactions, no adverse events have been associated with thimerosal in vaccines. However, in an effort to maintain high standards of safety and to enhance public confidence in vaccines, federal agencies and public health officials recommended that thimerosal be removed from vaccines. On July 7, 1999, the American Academy of Pediatrics (AAP) and the US Public Health Service (PHS) jointly announced that they would collaborate with the FDA and vaccine manufacturers to make sure that thimerosal was removed from all vaccines.[2] As mentioned above, today all recommended childhood vaccines for children age six years of age or younger are now available thimerosal-free.[3]

Recently, the question has been raised as to whether or not the use of vaccines containing thimerosal might cause neurodevelopmental disorders, specifically autism, attention deficit/hypersensitivity disorder and speech and language delay. While thimerosal-free vaccines are now available, the question remains whether the past inclusion of thimerosal in vaccines may have caused neurodevelopmental problems in some children. In addition, thimerosal-containing vaccines remain in use in the developing world where use of multi-dose vials of vaccine require this preservative.

Temporal relationship?

Some individuals experience local skin reactions such as redness and swelling or hypersensitivity reactions such as contact allergy following injection with products containing thimerosal.[1,4,5] The prevalence of thimerosal hypersensitivity in selected populations varies from 1% to 18%. There is a predominance in young adults, particularly those 20 to 30 years of age.[6]

Strength of Association?

Phase I of a Vaccine Safety Datalink Project study screened a health maintenance organization's (HMO's) records for potential associations between thimerosal-containing vaccines and selected outcomes. A statistically significant but weak association was found between various cumulative exposures to thimerosal-containing vaccines and unspecified developmental delays, tics, attention deficit disorder, language and speech delay and general neurodevelopmental delays. No association was found between exposures to thimerosal and other neurological disorders, including

GLOSSARY TERMS

Advisory Committee on Immunization Practices
Allergy
Association
Attention deficit disorder
Autism
Cases
Chelation therapy
Chronic
Coma
Disease
Dose response relationship
DTaP
Ethyl mercury
Haemophilus influenzae type b
Hepatitis
Hepatitis B
Hypersensitivity
Immunization
Influenza
Institute of Medicine
Measles
Methyl mercury
Neurodevelopmental disorders
Pertussis
Phase II study
Pneumococcal polysaccharide
Prevalence
Rabies
Risk
Seizure
Temporal relationship
Tetanus
Thimerosal
Toxic shock syndrome
Vaccine
Vaccine Safety Datalink Project
Varicella

ACRONYMS

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
ATSDR	Agency for Toxic Substances and Disease Registry
DTaP	Diphtheria, tetanus, acellular pertussis
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
Hib	*Haemophilus influenzae* type b
HMO	Health maintenance organization
IOM	Institute of Medicine
NIH	National Institutes of Health
PHS	United States Public Health Service
WHO	World Health Organization

WEB RESOURCES

National Partnership for Immunization
http://www.partnersforimmunization.org/issues.html

National Immunization Program
http://www.cdc.gov/nip/vacsafe/concerns/thimerosal

Johns Hopkins University's Institute of Vaccine Safety
http://www.vaccinesafety.edu

Immunization Action Coalition
http://www.immunize.org/thimerosal

Food and Drug Administration
http://www.fda.gov/bbs/topics/news/2001/new00756.html

autism or renal disorders.[7, 8] Reanalysis of these data generated results that differed slightly from the original analysis. However, the magnitude of the associations was generally consistent with those in the preliminary analysis.

A second component of this study was designed to test the hypotheses generated in the first phase. A sufficient number of cases of attention deficit/hypersensitivity disorder and speech delays were available for analyses. No significant differences in the risk of developing either attention deficit/hypersensitivity disorder or speech delays was found comparing persons who had been vaccinated with thimerosal-containing vaccines and those who had not. But because the sample size of this study was small the study is limited in its ability to detect whether these disorders might be found in a very small percentage of the population.[8,9]

Dose-response relationship?

Low-dose exposure of humans to either thimerosal or ethyl mercury, such as that received from vaccines, has not been demonstrated to be associated with effects on the nervous system. Instead, only hypersensitivity reactions such as contact allergy have been reported.[4, 5] The hypothesis that thimerosal exposure through the recommended childhood immunization schedule has caused neurodevelopmental disorders is not supported by clinical or experimental evidence.

Extremely high-dose exposure to thimerosal[10-15] and ethyl mercury[16-20] have been reported to produce toxic effects. Persons exposed to high doses of either thimerosal or ethyl mercury experienced mainly neurologic symptoms, including restlessness, slurred speech, confusion, unsteady gait, coma, impaired vision, hand tremors and death.

Prenatal exposure to low doses of methyl mercury has also been associated in some studies with subtle neurodevelopmental abnormalities.[21] Two large prospective studies are currently examining methyl mercury exposure from consumption of pilot whale meat in the Faroe Islands and from consumption of ocean fish in the Republic of Seychelles. In the Faroe Islands, a group of 1,000 children born in 1986-1987 are being followed through seven years of age. Analyses so far have found that prenatal exposure to methyl mercury based on measurement of the mercury content of the umbilical cord blood at the time of birth is associated with subtle attention, memory and language deficits.[22, 23] Two groups of over 700 children being followed in Seychelles have found no adverse associations between prenatal or postnatal exposure to methyl mercury and childhood developmental outcomes through 5.5 years of age. Exposures were determined by measuring the mercury concentration in maternal and child hair.[24-26]

Replication of findings?

Several agencies, including the EPA, Agency for Toxic Substance and Disease Registry (ATSDR), FDA and World Health Organization (WHO), have developed guidelines for intake of methyl mercury. A significant safety margin was incorporated into all federal mercury exposure guidelines.[27] The methyl mercury exposure limits calculated by these agencies are not considered to be the limits above which injury is certain to occur. Rather, they are general limits of exposure below which these organizations are confident that adverse effects will not occur.[4] Although the total amount of mercury found in all recommended childhood vaccines exceeded EPA guidelines,[21] which incorporates a ten-fold safety margin, they did not exceed guidelines recommended by the FDA (the agency responsible for the safety of vaccines), ATSDR[28] and WHO.[29]

Biologic plausibility?

At high doses, mercury compounds are well-established to be toxic to the nervous system.[28,30,31] Methyl mercury has been of particular concern to the public because high doses have been associated with health effects.[32] Two groups are most vulnerable to the effects of methyl mercury: the fetus and pregnant women. If a pregnant woman ingests methyl mercury at high concentrations, the developing fetus may develop brain damage, mental retardation, lack of coordination, blindness, seizures and an inability to speak. Premature babies are more vulnerable because they tend to be very small and their brain is not as developed as a full term baby. Because the guidelines for mercury exposure are based on amount of mercury per weight, children may be at greater risk of mercury exposure than are adults. This increased risk is due to greater exposure per pound of body weight and because children may be inherently more sensitive than adults as their nervous systems are still developing.[1] These serious health concerns led federal agencies to develop intake guidelines for methyl mercury.

No guidelines have been established for the ethyl mercury found in thimerosal, but experts agree that methyl mercury guidelines are appropriate to use when evaluating ethyl mercury. However, differences between methyl and ethyl mercury and their effects have been shown. Ethyl mercury is converted faster than methyl mercury into mercuric mercury.[10] Studies in mice have found that after administration of ethyl mercury more mercury was found in the blood and kidney—compared with methyl mercury—and less in the brain than after administration with methyl mercury.[33] Because of this faster conversion, researchers believe that ethyl mercury may remain in the body for a shorter period of time and be eliminated faster by urination than methyl mercury.[4]

Once both ethyl and methyl mercury reach the brain they are metabolized to the inorganic compound mercuric mercury. Ethyl mercury that enters the brain is more rapidly converted to mercuric mercury than methyl mercury that enters the brain. But once these compounds have been converted to mercuric mercury in the brain, they do not as readily cross the blood-brain barrier to move into the bloodstream for elimination.[4]

The Institute of Medicine (IOM) Immunization Safety Review Committee concluded that although the proposed association between exposure to thimerosal-containing vaccines and neurodevelopmental disorders has not been established, the hypothesis is biologically plausible.[4]

Consideration of alternative explanations?

Many causes of various neurodevelopmental disorders, such as genetic and environmental factors, have been hypothesized.[4] Some of these have been discussed in the *Autism* section on page 74.

Cessation of exposure?

The trace amounts of mercury contained in vaccines have not been found to cause any serious health problems in infants or young children. Recent studies by the National Institutes of Health (NIH) showed that the levels of mercury contained in the blood of immunized children are similar to those in unimmunized children.[34]

AAP, the Advisory Committee on Immunization Practices (ACIP) and the Surgeon General all recommend that parents do not let their children miss a vaccination when safe and effective vaccines are available. The risks of not vaccinating children far outweigh the unknown and probably much smaller risk, if any, of cumulative exposure to thimerosal-containing vaccines over the first six months of life.[2, 35]

Specificity of exposure?

Other than local hypersensitivity reactions, there is no evidence of any harm caused by the level of exposure that children may have encountered when immunized with thimerosal-containing vaccines under the existing immunization schedule.[1]

The acceptable levels of mercury exposure calculated by the EPA were based upon studies of children of women who had chronically ingested fish containing high levels of methyl mercury. These studies were then used to extrapolate acceptable levels of exposure of young children to trace levels of ethyl mercury contained in vaccines.[27] These EPA studies are under continuing scrutiny and have been criticized on a variety of scientific grounds.[36,37]

Consistency with other knowledge?

Some researchers have proposed that the similarities between autism and the toxic effects of mercury are evidence of an association.[38] However, the mechanisms causing these similar symptoms vary. For example, impaired ability to focus vision is associated with both mercury toxicity and autism. However, in the case of mercury toxicity, this impairment is due to problems with motor control of eye muscles. But in the case of autism, the visual impairment is related to joint use, which is most likely a problem of social reciprocity, not motor control.[4]

Another argument that has been made for the proposed association between thimerosal and autism is based on the observation that some autistic children have abnormal blood-metal profiles. But the presence of abnormal metal profiles in autistic children does not mean that the metal burden is the cause of autism. An inability to metabolize heavy metals such as mercury may occur as a result of autism rather than the cause of the disease. Further, a favorable response to chelation therapy (therapy used to reduce the concentration of metals in the blood) is not proof that the mercury levels caused the neurological dysfunction. Chelation therapy is non-specific, and the observed effects could be caused by the removal of other metals or by other factors.[4]

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Diabetes

Diabetes is a condition that prevents the body from being able to make enough insulin and/or being able to use the insulin that the body does make. Insulin is needed to help the body to use sugar absorbed from the bloodstream. People with diabetes have high blood sugar levels. Type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), is an autoimmune disease that occurs primarily in children, but the disease has been found in persons of all ages.[1]

A 10-year follow-up of Finnish children who participated in a trial of the safety and effectiveness of the *Haemophilus influenzae* type b (Hib) vaccine looked at the possible association between this vaccine and type 1 diabetes. The study concluded that no significant relationship existed between the vaccine and diabetes.[1] However, another researcher analyzed the same data and claimed that an association did exist.[2] This sparked concern about whether a relationship between the two does exist and about whether the timing of hepatitis B vaccine delivery, which coincides with the Hib schedule, may affect the risk of developing diabetes.[3] However, the association between hepatitis B vaccine and/or other vaccines and IDDM has been refuted by many immunization experts and safety studies as noted below.

Temporal relationship?

One report suggests that the greatest increase in type 1 diabetes in New Zealand occurred in children under four years of age, coinciding with the period when Hib vaccine was introduced there in the mid-1980s.[4] However, figures from these studies show that cases of diabetes have continued to increase from 1976 to 1996, with one new case every two years. These figures suggest that the introduction of the hepatitis B vaccine in 1987/88 did not alter this rate of increase.[5]

Strength of association?

A 1999 Finnish study reported a relative risk of 1.01 (essentially no risk) of developing type 1 diabetes when comparing children born before the vaccination period with those vaccinated at 24 months of age.[1] Reanalysis of these data by another research group found an increased relative risk of 1.26 when they compared those children receiving vaccine and those not receiving the vaccine, which indicates only a small increased risk of developing diabetes.[4]

Replication of findings?

The only evidence suggesting a possible association between the risk of developing diabetes and vaccination has come from one research group.[6, 7] Based on animal experiments and on comparisons of diabetes rates between countries with different immunization schedules, this group suggested that certain vaccines given at birth may decrease the chance of developing diabetes as compared to vaccination after two months of age.[6] Researchers who have examined the relationship between vaccination and diabetes without regard to time of administration have not found an increased risk of diabetes with vaccination.[8-12]

In 1998, a review of the current state of knowledge of IDDM and its possible links to human vaccination was published. Evidence of a causal link in humans was examined by reviewing 12 large trials and two meta-analyses of pediatric vaccines. This review found that the international scientific literature was insufficient to determine whether a possible link exists between onset of IDDM and vaccination.[13]

An Institute for Vaccine Safety Workshop in March 1998, concluded that no vaccines have been shown to increase the risk of type 1 diabetes in humans. Workshop participants included 30 experts on the pathogenesis of diabetes, autoimmune disease, epidemiology, biostatistics, vaccines and adverse events associated with vaccines.[14]

A study of more than 1,000 children born in the health maintenance organizations (HMOs) involved in the Vaccine Safety Datalink Project from 1988 through 1997 observed that children vaccinated against hepatitis B virus or Hib were not at

GLOSSARY TERMS

Adverse events
Association
Autoimmune disease
Beta cell
Biostatistics
Cases
Diabetes
Disease
Haemophilus influenzae type b
Hepatitis
Hepatitis B
Hib vaccine
Immunization
Incidence
Insulin
Insulin-dependent diabetes mellitus
Non-obese diabetic mice
Pathogenesis
Relative risk
Risk
Temporal relationship
Type I diabetes
Vaccine
Vaccine Safety Datalink Project
Virus

ACRONYMS

DTaP	Diphtheria, tetanus, acellular pertussis
Hib	*Haemophilus influenzae* type b
HMO	Health maintenance organization
IDDM	Insulin-dependent diabetes mellitus
NOD	Non-obese diabetic

WEB RESOURCES

American Diabetes Association
http://www.diabetes.org/main/community/info_news/news/vaccines.jsp

National Partnership for Immunization
http://www.partnersforimmunization.org/issues.html

National Immunization Program
http://www.cdc.gov/nip/vacsafe/concerns/diabetes

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/concerns.shtml

increased risk of developing type 1 diabetes. Furthermore, the age at which the children were vaccinated was not likely to affect the risk of developing the disorder.[3,15]

Biologic plausibility?

A possible link between hepatitis B vaccination and insulin-dependent diabetes mellitus (IDDM) was first suggested after the demonstration of a relationship between the timing of administration of the DTP vaccine and the development of IDDM in non-obese diabetic (NOD) mice.[5] However, findings from animal studies[7] cannot be directly applied to people due to large biological differences between the two, in part because most NOD mice are genetically predisposed to developing IDDM.[16]

Consideration of alternative explanations?

Other genetic and environmental triggers for the development of IDDM have been suggested and continue to be explored. Damage to the pancreatic beta cells has been found to lead to type 1 diabetes in genetically susceptible individuals. This damage is believed to be induced by environmental factors.[1]

Cessation of exposure?

In the absence of evidence of a causal relationship between immunizations and the development of diabetes, the risks of developing diabetes are unlikely to be altered by eliminating or modifying the existing childhood immunization schedule. Reducing or eliminating the immunization of children have in the past resulted in outbreaks of vaccine-preventable diseases.[17]

Specificity of the association?

Although the incidence of diabetes is increasing throughout the world, the increase has occurred in countries with or without the introduction of new vaccines.[18]

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Multiple Sclerosis (MS)

Multiple sclerosis (MS) is a neurologic disorder associated with autoimmune-mediated destruction of myelin, the coating of the nerve fibers of the brain and spinal cord. Depending on the extent and location of destroyed coating, a wide range of symptoms result.[1] Although neurologists are aided by magnetic resonance imaging (MRI), analysis of the fluid obtained by lumbar puncture and other techniques in the identification of this disease,[1] diagnosis of MS is usually made after multiple occurrences of traditional symptoms.[2]

In the US, approximately 300,000 individuals have been diagnosed with MS. The highest incidence of disease is between the ages of 20 and 40 years. More women than men are affected, and MS is found more frequently in Caucasians than in other ethnic groups.[3]

The history of concern over the potential association between MS and vaccination with hepatitis B vaccine began following the 1994 initiation of a national immunization campaign targeting newborns and adolescents in France. An increasing number of reports suggesting that MS might develop within months of vaccination with hepatitis B vaccine led to increased public concern in France about this issue and to the launch of epidemiological studies to investigate a possible association between hepatitis B vaccination and MS.[4]

Temporal relationship?

Much of the available information suggesting this potential association is based upon the number of cases of MS or other demyelinating diseases occurring after vaccination that were reported to French health authorities and vaccine manufacturers.[1] Despite these reports, French data collected through June 1998 show a rate of 0.6 case of MS per 100,000 persons vaccinated, which is a lower rate than the expected incidence in the same population (estimated at one to three cases per 100,000 population).[1, 5]

A case for a temporal relationship between the hepatitis B vaccine and MS might be made if, following the introduction of the hepatitis B vaccine in a certain area, the average age of developing MS in that area became closer to the recommended age for hepatitis B vaccination. A case might also be made if after the introduction of the hepatitis B vaccine in a population the proportion of males and females with the disease within that population began to mirror the rates of vaccination with hepatitis B vaccines within each sex. The average age of people with MS and the distribution of this disease among males and females has not changed with the introduction of the hepatitis B vaccine in the US.[2,6]

Results of a study utilizing Vaccine Safety Datalink Project data to evaluate the timing of hepatitis B vaccination and the risk of developing MS did not find that vaccination triggered the development of MS.[7]

Strength of the association?

A case-control study was conducted in two large cohorts of nurses in the US. The analyses included 192 women with MS and 645 matched controls (534 healthy controls and 111 with breast cancer). The relative risk of MS associated with exposure to the hepatitis B vaccine at any time before the onset of the disease was 0.9. The relative risk associated with hepatitis B vaccination within two years before the onset of MS was 0.7.[5]

A study of Vaccine Safety Datalink Project data also assessed the association between hepatitis B vaccination and the development of demyelinating diseases of the central nervous system in adults. The immunization status of 440 participants with MS were compared with that of 950 matched controls. The relative risk of developing MS associated with hepatitis B vaccination was 0.8 using a doctor's diagnosis and 0.9 using a specialist's diagnosis. Results did not support the hypothesis that hepatitis B vaccination causes or triggers the development of MS.[7]

GLOSSARY TERMS

Acute
Acute disseminated encephalomyelitis
Amino acids
Antigen
Association
B cell
Bacteria
Bystander activation
Case control study
Cases
Controls
Demyelinating
Disease
Dose response relationship
Epidemiological studies
Etiology
Experimental autoimmune encephalomyelitis
Hepatitis
Hepatitis B
Immune system
Immunization
Incidence
Inflammation
Influenza
Institute of Medicine
Interferon gamma
Lumbar puncture
Macrophage
Magnetic resonance imaging
Measles
Molecular mimicry
Multiple sclerosis
Mumps
Myelin
Neurologic disorder
Polymerase protein
Prevalence
Protein
Rabies
Relative risk
Risk
Rubella
Superantigens
T cell
Temporal relationship
Vaccine
Vaccine Safety Datalink Project
Varicella
Virus

ACRONYMS

ADEM	Acute disseminated encephalomyelitis
EAE	Experimental autoimmune encephalomyelitis
IOM	Institute of Medicine
MMR	Measles, mumps, rubella
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
WHO	World Health Organization

WEB RESOURCES

National Partnership for Immunization
http://www.partnersforimmunization.org/issues.html

National Immunization Program
http://www.cdc.gov/nip/vacsafe/conerns/MS/default.htm

Johns Hopkins University's Institute for Vaccine Safety
http://www.vaccinesafety.edu/hepb-nejm.htm

Multiple Sclerosis Foundation
http://www.msfacts.org

National Multiple Sclerosis Society
http://www.nmss.org

Vaccine Education Center at The Children's Hospital of Philadelphia
http://www.vaccine.chop.edu/concerns.shtml

Two unpublished case control studies performed in England and France reported a statistically non-significant relative risk of 1.4 linking the hepatitis B vaccine with the occurrence of demyelinating disease within a period of two months after vaccination.[1]

Dose-response relationship?

In a case-control study of US nurses, no association was found between the number of doses of vaccine received by an individual and an increased risk of MS.[5]

Replication of findings?

The Institute of Medicine (IOM) Immunization Safety Review Committee found that currently available epidemiological evidence favors rejection of a causal relationship between the hepatitis B vaccine use by adults and MS.[8]

A group of international experts convened by the World Health Organization (WHO) met in 1998 to examine all of the post-marketing surveillance studies from the different vaccine manufacturers in North America. None of these studies showed any evidence of an increased risk of MS.[6]

Biologic plausibility?

Theoretical biological mechanisms that might explain an association between MS and hepatitis B vaccination include the concepts of molecular mimicry, bystander activation and superantigens (see the discussion of autoimmunity in the section *Multiple Immunizations*). These mechanisms have been demonstrated in mouse studies of experimental autoimmune encephalomyelitis (EAE), the archetypal model for MS.[8]

Molecular mimicry refers to immunologically similar microbial antigenic determinants and self antigens that when recognized by the immune system, can lead to autoimmune destruction of the host tissue.[9] No such similarity exists between the amino acid sequences of the hepatitis B surface antigen, the main component of the hepatitis B vaccine and the proteins making up human nerve fibers.[2] Animal studies have shown that a part of rabbit myelin shares six consecutive amino acids with a hepatitis virus polymerase protein and causes brain inflammation when injected in a rabbit.[1] But a relationship has not been found between hepatitis B virus polymerase protein and human myelin. Likewise, the hepatitis B vaccine does not contain the polymerase protein from the hepatitis B virus.[1]

Bystander activation refers to the non-specific stimulation of inflammatory cells associated with the normal response to an infection. Upon activation, these cells release large quantities of cytokines and other factors that contribute to the destruction of host tissue. Superantigens, natural proteins produced by certain viruses and bacteria, may also activate T cells, B cells or macrophages to cause destruction of myelin in mice.[10] However, no conclusive evidence exists that molecular mimicry, bystander activation or superantigens cause MS onset or MS exacerbations.[2]

Consideration of alternative explanations?

Infection by known or unknown organisms often precedes the onset of MS, MS relapses and/or MS exacerbations. Most researchers believe that MS disease progression results from a combination of infection and autoimmune events in genetically susceptible individuals.[9]

For the past 100 years, many different infections and viruses have been suggested as possible causes of MS. However, none of these hypotheses has been accepted because intensive scientific investigation has failed to demonstrate any causal relationships.[11] But data have shown that multiple factors, including genetic and environmental factors, can contribute to the development of this disease.[1]

Evidence exists of genetic involvement in the development of MS. Parents and siblings of MS patients have a 10 to 20 times greater risk of developing the disease than does the general population. In fact, 15% to 20% of persons with MS have another family member who has the disease. While 30% to 35% of identical (having the same genetic make-up) twins either both have MS or both do not have MS, only 2% to 5% of fraternal (do not have the same genetic make-up) twins either both have MS or both do not.[2] Although one particular region on chromosome 6p21 has been strongly associated with MS, studies have suggested that as many 15 to 20 other genomic regions may contribute to MS susceptibility.[12]

Environmental impacts on MS disease have been demonstrated by several epidemiological studies showing that individuals who migrated after age 15 from regions of high disease prevalence to regions of low disease prevalence, or vice versa, carry their native risk for contracting MS.[13,14] Further environmental involvement is suggested by reports of localized clusters, defined areas of unexpected high prevalence of MS and a higher prevalence of disease in the northern latitudes.[2]

Psychological stress,[15] immediate post-partum upper respiratory viral infections, interferon gamma, experimental drugs[2] and infections[8] have all also been implicated in causing MS relapses.

Cessation of exposure?

In the absence of evidence of a causal relationship between hepatitis B immunization and the development of MS, the risks of developing MS are unlikely to be altered by eliminating or modifying the existing immunization schedule. Reducing or eliminating immunization has in the past resulted in outbreaks of vaccine-preventable diseases.[16]

Specificity of the association?

Cases of MS in British Columbia were investigated in adolescents before and after the introduction of a grade six (11-12 year old students) hepatitis B vaccination program. Onset of MS among adolescents aged 11-17 years of age was determined from hospital medical records and the database of the provincial MS clinic. All pediatric neurologists in the province were also contacted to confirm that all cases known to them were assessed in the specified settings. Nine cases of adolescent-onset MS occurred among 288,657 students who had attended grade six prior to the vaccination campaign (January 1986 – September 1992) and five cases occurred out of a total of 289,651 grade six students from October 1992 to September 1998, of whom 267,412 (92.3%) completed the full hepatitis B vaccine series. These numbers were not significantly different.[17]

Consistency with other knowledge?

Infection with natural hepatitis B virus has not been proven to cause MS or to worsen clinical disease symptoms. If the virus does not cause MS or worsen existing disease, then the likelihood that the vaccine can do so is extremely low.[3,18]

Acute disseminated encephalomyelitis (ADEM) is a rare disease of the central nervous system that usually affects infants and young children. The disease is very similar to MS except that one episode of neurologic symptoms occurs rather than the multiple episodes characteristic of MS.[19] After the introduction of the first vaccine against rabies in humans, 0.1% of vaccinees were reported to have contracted ADEM. This vaccine was manufactured from rabbit cells containing rabies virus, and the immunization thus initiated the human equivalent of EAE.[2] Measles, rubella and varicella viruses and, less commonly, influenza and mumps viruses have been shown to cause ADEM. The incidence of ADEM after measles infection is approximately one out of 1,000 infections, whereas after varicella and rubella it is less than one out of 10,000 and one out of 20,000 respectively.

Despite the fact that vaccines do not contain this rabbit tissue anymore, ADEM is sometimes still reported after various vaccinations. The incidence of post-immunization ADEM is one to two per million for live measles vaccine immunizations, i.e., significantly lower than that for post-measles development of ADEM. It is most commonly associated with measles, mumps, rubella (MMR) vaccinations but more recently has been associated with two recombinant hepatitis B vaccines.[2]

A case-crossover study (equivalent to a case-control approach in which patients serve as their own controls) of 643 patients with relapses of MS between 1993 and 1997 in the European Database for Multiple Sclerosis was conducted to assess whether vaccinations increase the risk of relapse in MS. No increase in the relative risk of relapse associated with exposure to any vaccination during the previous one, two or three months was found.[18] This study did not address long-term effects of vaccination or changes in the etiology of the disease and excluded patients with frequent relapses (within one year of each other).[20]

No evidence exists that vaccines in children cause more or less frequent demyelinating disease than in adults.[2] In a retrospective study of 134,698 individuals enrolled in a US healthcare database from 1988 to 1995, the incidence of demyelinating diseases was not increased after hepatitis B vaccination in the general population or among children under age 14 years.[21] In another report, hepatitis B vaccine in children ages 11 to 12 years did not increase the risk of developing MS or ADEM in adolescence.[22]

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Shaken Baby Syndrome (SBS)

Shaken Baby Syndrome (SBS), a serious form of child maltreatment, usually involves infants less than six months of age and is often overlooked or underdiagnosed.[1] This medical condition is due to mechanical injury that can result in brain swelling and bleeding inside the brain or on the retina of the eye. Death or permanent brain damage are frequent outcomes in SBS. In recent years, a defense has surfaced in criminal cases involving SBS that alleges that the child was injured by an injection of diphtheria, tetanus, whole cell pertussis (DTP) vaccine. DTP vaccine is no longer used in the US as it has been replaced with diphtheria, tetanus, acellular pertussis (DTaP) vaccine.

Replication of findings?

Scientific studies have not provided evidence to support a causal relationship between DTP immunization and serious acute neurologic illness resulting in permanent neurologic injury.[2] An article from the United Kingdom dismisses the theory that pertussis vaccine can cause permanent brain damage in infants on scientific grounds.[3]

Biologic plausibility?

No medical reports have proposed that this pathology could be related to DTP immunization.[2]

Consideration of alternative explanations?

In highly contested child abuse criminal trials, even speculative possibilities can be sufficient to raise a reasonable doubt concerning a defendant's guilt, since juries do not want to believe that caretakers are capable of violent assault on helpless children.[2]

Cessation of exposure?

In the absence of evidence of a causal relationship between DTP immunization and SBS, the risks of SBS are unlikely to be altered by eliminating or modifying the existing immunization schedule. Reducing or eliminating immunization has in the past resulted in outbreaks of vaccine-preventable diseases.[4]

Specificity of the association?

The pathology and progression of SBS varies greatly from the adverse events that have been associated with DTP vaccine. Rare cases of inflammation of the brain and spinal cord have been reported following DTP vaccination, but the mechanical injuries seen in SBS are very different from these adverse events.[2]

GLOSSARY TERMS

Acute
Adverse events
Association
Cases
Cytokines
Disease
Immunization
Inflammation
Pathology
Pertussis
Risk
Shaken Baby Syndrome
Tetanus

ACRONYMS

DTaP	Diphtheria, tetanus, acellular pertussis
DTP	Diphtheria, tetanus, whole cell pertussis
SBS	Shaken Baby Syndrome

WEB RESOURCES

National Partnership for Immunization
http://www.partnersforimmunization.org/issues.html

National Center on Shaken Baby Syndrome
http://www.dontshake.com/sbsfall00dtp.html

American Academy of Pediatrics
http://www.aap.org/policy/t0039.html

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GLOSSARY AND ACRONYMS

GLOSSARY

Acellular vaccines: Vaccines containing partial cellular material as opposed to complete cells.

Acquired immunity: Antibody and cell-mediated immune responses specific to a particular pathogen (and perhaps some of its close relatives) that can result in either short-term or long-term protection. These responses involve a variety of types of cells found in the blood and tissues and can require a week or more to become established.

Acute: A short-term, intense health effect.

Acute disseminated encephalomyelitis: Rare disease of the central nervous system, which usually affects infants and young children. The disease is very similar to multiple sclerosis (MS) except that one episode of neurologic symptoms occurs rather than the multiple episodes characteristic of MS.

Acute otitis media: A viral or bacterial infection that leads to inflammation of the middle ear. This condition can occur following pneumococcal disease. Symptoms include earache, high fever, nausea, vomiting and diarrhea. In addition, hearing loss, facial paralysis and meningitis may result.

Adjuvant: An additive to a vaccine that increases its effectiveness in producing antibodies against a disease-causing agent.

Adverse events: Undesirable experiences occurring after immunization that may or may not be related to the vaccine. Adverse events can range from minor effects such as tenderness at the site of injection and mild fever to rare, serious effects such as seizures and serious allergic reactions.

Advisory Committee on Immunization Practices (ACIP): This committee consists of 15 immunization experts that develop written recommendations for the routine administration of vaccines to the public. ACIP also develops the schedules that note the appropriate timing, dosage and contraindications for each vaccine.

Allergic reaction: Sneezing, itching and/or skin rashes or other reactions caused by the body's abnormal immune response to certain substances.

Allergy: A condition in which the body has an exaggerated immune response to a substance, e.g., food or drug. Also known as hypersensitivity or an allergic reaction.

Amino acid: A class of chemical compounds that link together to form proteins. Often called the building blocks of a cell.

Anaphylaxis: An immediate and severe allergic reaction to a substance, e.g., food or drugs. Symptoms of anaphylaxis include breathing difficulties, loss of consciousness and a drop in blood pressure. This condition can be fatal and requires immediate medical attention.

Anorexia: Refers to the loss of body weight.

Anthrax: An acute infectious disease caused by the large, spore-forming bacterium *Bacillus anthracis*. Naturally occurring disease in humans is acquired by skin contact, ingestion or inhalation of *Bacillus anthracis* spores from infected animal products or inhalation of spores from the environment. Human anthrax is not contagious and therefore cannot be transmitted from one person to another. Three forms of this disease exist in humans: cutaneous (skin), gastrointestinal and inhalational (lung) anthrax.

Antibiotic: Medicine that is produced by microorganisms and is capable of destroying or weakening particular bacteria.

Antibody: A protein found in the blood that is produced in response to foreign substances, e.g., bacteria or viruses, invading the body. Antibodies protect the body from disease by binding to these organisms and destroying them.

Antigen: Foreign substance, e.g., bacteria or viruses, in the body that is capable of causing disease. The presence of antigens in the body triggers an immune response, usually the production of antibodies and cytotoxic T cells.

Arthralgia: Joint pain.

Arthritis: A medical condition characterized by inflammation of the joints, which results in pain and difficulty in moving.

Aseptic meningitis: Meningitis that occurs in the absence of an infecting organism. It can be due to a diagnostic or therapeutic procedure, a tumor or other non-infectious agents within the skull or spinal canal.

Asperger's disorder: A type of autism-spectrum disorder characterized by normal early language skills and intelligence levels along with problems with social and motor skills.

Association: The degree to which the occurrence of two variables or events are linked. Association describes a situation where the likelihood of one event occurring depends on the presence of another event or variable. However, an association between two variables does not necessarily imply a cause and effect relationship. The term association and relationship are often used interchangeably. See causal and temporal association.

Asthma: An allergic reaction that is localized to the lungs and airways and may be manifested by wheezing, dyspnea and respiratory insufficiency.

Attack rate: The proportion of persons who develop a disease relative to the total number of persons at risk for developing the disease.

Attention deficit disorder: A childhood syndrome characterized by impulsiveness, hyperactivity and short attention span, which often leads to learning disabilities and various behavioral problems.

Attenuated vaccines: Vaccines in which a live virus is weakened through chemical or physical processes in order to produce an immune response without causing the severe effects of the disease.

Attributable risk: The amount or proportion of disease that can be said to be caused by a specific exposure.

Autism: A chronic developmental disorder usually diagnosed between 18 and 30 months of age. Symptoms include problems with social interaction and communication as well as repetitive interests and activities.

Autism-spectrum disorders (ASD): Term used to describe the range of functioning among persons with autism.

Autoimmune disease: Disease that occurs when a person's antibodies or lymphocytes attack their own cells and/or tissues.

B cell: Small white blood cell that helps the body defend itself against infection. This cell is produced in bone marrow and develops into plasma cells which produce antibodies. Also known as a B-lymphocyte.

Bacillus anthracis: Spore-forming bacterium that causes anthrax.

Background incidence: The rate of disease in the general population that exists regardless of the exposure in question.

Bacteria: Tiny one-celled organisms present throughout the environment that require a microscope to be seen. While not all bacteria are harmful, some cause disease. Examples of bacterial disease include diphtheria, pertussis, tetanus, *Haemophilus influenza* and pneumococcus (pneumonia).

Bacteremia: The presence of bacteria circulating in the bloodstream that are capable of growing or reproducing.

Bacterial meningitis: Meningitis caused by bacteria.

Beta cell: Insulin-producing cell found in the pancreas.

Bias: Any factor or consideration that consciously or unconsciously enters into the design or interpretation of a scientific study that would predispose the study to reach a predetermined or desired conclusion.

Biostatistics: Statistical methods and processes applied to the analysis of biological data.

Blinded: Description of researchers who are kept unaware of key information (such as exposures and diagnoses) regarding research study participants for the purpose of remaining unbiased in reporting study findings and in making study conclusions.

Blood serum: Yellowish fluid that separates from a blood clot after coagulation.

Booster: A second, third or greater immunization with a specific vaccine that may be necessary to ensure that the individual is protected against the infectious disease.

Bordetella pertussis: Rod-shaped bacteria that cause pertussis (whooping cough).

Bovine spongiform encephalopathy (BSE): Fatal neurological disease of cattle that was first identified in 1986. The disease is thought to be spread through cattle feed containing meat and bone meal from infected cows and causes apprehension, loss of orientation and movement disturbances that can lead to frenzied behavior.

Breakthrough cases: Persons who develop a vaccine-preventable disease even though they have been immunized and their immune system has responded to the vaccine. Breakthrough cases in vaccinated persons tend to be less serious than natural disease in unvaccinated persons.

Bystander activation: Non-specific stimulation of inflammatory cells that are associated with the normal response to an infection. Upon activation, these cells release large quantities of cytokines and other factors that contribute to the destruction of host tissue.

Case ascertainment: The determination through diagnostic methodology of whether or not a person is infected with a particular disease.

Case-control studies: Studies in which researchers identify a group of persons with the disease (cases) and a group of persons without the disease (controls) and then determine the proportion of each group that were exposed to the proposed risk factor.

Cases: A group of persons in a research study who have been exposed to the proposed risk factor, i.e., the vaccine.

Case series: Research studies that select and characterize cases exposed to the proposed risk factor but do not use a control group.

Cataracts: A clouding of the lens of the eye or of its surrounding transparent membrane causing an obstruction in the passage of light into the eye.

Causal association: The presence or absence of a variable, e.g., smoking, is responsible for an increase or decrease in another variable, e.g., cancer. A change in exposure leads to a change in the outcome of interest.

Cell-mediated response: Immune response provided by the direct action of immune cells (as distinct from the response provided by antibodies and other soluble molecules).

Cellulitis: Diffuse inflammation of body connective tissue located under the skin.

Cerebral palsy: Disability resulting from damage to the brain before or during birth causing muscular incoordination and speech disturbances.

Chelation therapy: Non-specific therapy used to reduce the concentration of metals in the blood.

Chemokines: Certain chemicals that are released by cells surrounding an area of injury or pathogen attack that help to direct the immune response.

Chickenpox: A severe, contagious viral infection, which is characterized by red blotches appearing on the skin. The infection is transmitted by airborne droplets and direct contact with lesions. Complications include bacterial infection of skin lesions, pneumonia, dehydration, hospitalization and death. Also known as varicella.

Childhood developmental disorder: A type of autism-spectrum disorder characterized by a period of normal development followed by a marked regression with only minimal recovery.

Chronic: A disease or health condition that lasts for a long period of time, e.g., cancer, asthma.

Chronic carrier: Person who remains infected with a disease agent and therefore may be able to pass the disease agent to persons they come into contact with. Chronic carriers may or may not exhibit disease symptoms.

Chronic obstructive pulmonary disease: Long-term, persistent blockage of air flow into and out of the lungs.

Cirrhosis: A chronic disease of the liver characterized by the formation of nodules and scar tissue.

Clinical trial: Research studies in which human are exposed to vaccines or pharmaceutical compounds under the direct supervision of physicians, nurses or other health care professionals.

***Clostridium tetani*:** Rod-shaped bacteria that cause tetanus.

Cohort studies: Studies in which researchers select a group of individuals that are exposed to the proposed risk factor and a group of individuals that are not exposed to the proposed risk factor, and follow both groups to compare the incidence of disease (or rate of death from the disease) in the two groups.

Coma: A state of unconsciousness caused by disease, injury or poison.

Combination vaccine: Two or more vaccines administered in a single injection in order to reduce the number of shots given. For example, the MMR (measles, mumps, rubella) vaccine.

Community immunity: Having a large percentage of the population vaccinated in order to prevent the spread of certain infectious diseases. Even individuals not vaccinated (such as newborns and those with chronic illnesses) are offered some protection because the disease has little opportunity to spread within the community. (Also known as herd immunity.)

Compulsory immunization laws: State laws that require children to receive certain vaccines before they are allowed to enter school.

Confounder: A factor that must be taken into account when designing or interpreting a scientific study. Failure to consider confounding factors can lead to misinterpretation of the results.

Congenital rubella syndrome: Infection of a developing fetus that can lead to death, premature delivery, deafness, cataracts, heart defects, abnormalities of the nervous system, mental retardation, bone alterations and liver and spleen damage.

Congestive heart failure: A heart condition in which blood accumulates in the heart leading to insufficient circulation of the blood through the rest of the body.

Conjugate vaccine: The joining together of two compounds (usually a protein and a polysaccharide) to increase a vaccine's effectiveness.

Contraindications: Condition or symptom that makes a particular treatment or procedure inadvisable.

Controls: A group of persons in a research study who have not been exposed to the proposed risk factor, e.g., the vaccine.

Corynebacterium diphtheriae: Rod-shaped bacteria that cause diphtheria.

Coverage: Refers to the proportion of persons in a population that have received the full course of specific immunizations recommended by the Advisory Committee on Immunization Practices (ACIP).

Coxsackievirus: Any of a group of viruses that attacks the gastrointestinal tract that can cause a disease resembling poliomyelitis but without paralysis.

Creutzfeldt-Jakob disease: Human neurodegenerative disease associated with prion infection that progresses from memory loss and confusion, to behavioral and movement abnormalities, to a host of neurological deficits.

Crohn's disease: A chronic medical condition characterized by inflammation of the bowel. Symptoms include abdominal pain, diarrhea, fever, loss of appetite and weight loss. The cause of Crohn's disease is not known, but genetic, dietary and infectious factors may play a part in disease progression.

Cross-sectional studies: Research studies in which investigators determine both proposed risk exposure and disease outcome simultaneously.

Current Good Manufacturing Practices (CGMP): Minimum Food and Drug Administration (FDA) standards for the vaccine manufacturing process that specify quality control, documentation, testing and facility requirements that each vaccine manufacturer must meet both before a vaccine is licensed and for as long as it continues to be used by the public.

Cutaneous anthrax: Disease caused when *Bacillus anthracis* bacterium enters a cut or abrasion on the skin. Infections begin as a raised itchy bump resembling an insect bite and progress to a fluid-filled blister with a black area in the center.

Cytokines: Certain chemicals that are released by cells of the immune system surrounding an area of injury or pathogen attack that help to direct the immune response.

Cytomegalovirus: A member of the herpes virus group that may cause enlargement of the liver and spleen and lead to hearing loss, vision impairment or mental retardation in some infected persons.

Cytotoxic T cell: Type of lymphocyte that develops the ability to identify and destroy certain pathogens or pathogen-infected cells when it is stimulated by an antigen.

DEET: A chemical found in many mosquito repellents that provides effective and long-lasting protection against bites from mosquitoes and ticks.

Demyelinating: Destroying or removing the myelin sheath of a nerve fiber.

Deoxyribonucleic acid (DNA): A long, unbranched molecule of nucleotides containing deoxyribose that contain molecules for the production of proteins.

Diabetes: A chronic health condition where the body is unable to produce insulin and properly breakdown sugar (glucose) in the blood. Symptoms include hunger, thirst, excessive urination, dehydration and weight loss. The treatment of diabetes can require daily insulin injections, proper nutrition and regular exercise. Complications can include heart disease, stroke, neuropathy and poor circulation leading to loss of limbs, hearing impairment, vision problems and death.

Diphtheria: Serious infectious respiratory disease infecting the throat, tonsils and nose.

Diphtheria, Tetanus, acellular Pertussis vaccine (DTaP): A combination vaccine that protects against diphtheria, tetanus and pertussis (whooping cough).

Disease: Sickness, illness or loss of health.

Dose-response relationship: Criterion used in evaluating a causal relationship between a vaccine and an adverse reaction. If an association does exist the amount or number of doses of vaccine should theoretically increase at an identical or similar rate as the risk of the adverse event. The absence of a dose-response relationship does not necessarily rule out a causal relationship.

Dysenteric infection: Inflammatory infection of the lower intestinal tract that results in pain, fever and severe diarrhea, often accompanied by the passage of blood and mucus.

Dysfunction: Impaired or abnormal functioning.

Ecologic studies: Studies that examine group characteristics, often using data from such sources as registries, birth certificates, average values for disease rates, vaccine uptake, etc. These studies are often the first approach used by researchers in determining whether or not an association exists. However, because these studies use group data and cannot account for variability among individuals within a group, certain study characteristics may be incorrectly attributed to members of a group that do not in fact possess these characteristics as individuals. Therefore, ecologic studies alone cannot demonstrate that a causal association exists.

Eczema: An inflammatory condition of the skin characterized by redness, itching and oozing vesicles, which become scaly, crusted or hardened.

Efficacy: A measure used to describe how good a vaccine is at preventing the targeted disease.

Encephalitis: Inflammation of the brain caused by a virus. Encephalitis can result in permanent brain damage or death.

Encephalographic: Measurement of brain function through the recording of electrical signals from the brain under various conditions, e.g., resting, sleeping, problem solving, etc.

Encephalopathy: A general term describing diseases of the brain, including degenerative changes. Examples include encephalitis, meningitis, seizures and head trauma.

Endemic: Native to a particular people or country.

Endotoxin: Chemicals associated with certain bacteria that cause fever and other symptoms of infection.

Enterocolitis: Inflammation of both the large and small intestines.

Eosinophil: A type of white blood cell that contains granules that are easily stained (for identification purposes) by dyes.

Epidemic: The occurrence of disease within a specific geographical area or population that is in excess of what is normally expected.

Epidemiologic studies: Studies of how disease is distributed in populations and of the factors that influence or determine this distribution.

Epiglottitis: Inflammation of the epiglottis, a flap of tissue that covers the trachea (air passageway) when swallowing to prevent food and liquid from entering or blocking a person's airway and obstructing normal breathing.

Erythema: Redness of the skin caused by dilation and congestion of the blood vessels, often a sign of inflammation or infection.

Ethyl mercury: The form of mercury found in thimerosal.

Etiology: The cause or origin of a disease or disorder as determined by medical diagnosis.

Excise taxes: Tax levied by the federal government on the sale of certain products in the United States. In the case of vaccines, the revenue derived from the excise tax is used to fund the Vaccine Injury Compensation Program.

Exemptors: Individuals who refuse vaccination on religious or philosophical grounds.

Experimental autoimmune encephalomyelitis: Mouse disease that was the original research model for studying the human disease of multiple sclerosis.

Fragile X syndrome: Inherited disease caused by a gene mutation. Symptoms include: mental impairment, attention deficit, hyperactivity, anxiety and unstable mood, autistic-like behaviors, long face, large ears, flat feet, hyperextensible joints and seizures.

Gastroenterology: The study of the diseases and pathology of the stomach and intestines, i.e., the digestive tract.

Gastrointestinal anthrax: Anthrax disease that occurs when a person ingests insufficiently cooked, contaminated meat. Infection results in an acute inflammation of the intestinal tract.

Gastrointestinal system: Includes the stomach and the intestines.

Gastrointestinal tract: Starts from the mouth and continues to the esophagus, stomach, duodenum, small intestine, large intestine, rectum and anus.

Genome: One set of half the number of characteristic chromosomes in a person's body along with the genes they contain.

German measles: Another name for rubella.

Group A streptococcus: Diverse group of round bacteria associated with respiratory and other infections. These diseases are not currently vaccine-preventable.

Guillain-Barré syndrome (GBS): A rare neurological disease characterized by loss of reflexes and temporary paralysis. Symptoms include weakness, numbness, tingling and increased sensitivity that spreads over the body. Muscle paralysis starts in the feet and legs and moves upwards to the arms and hands. Sometimes paralysis can occur in the respiratory muscles causing breathing difficulties. Symptoms usually appear over the course of one day and may continue to progress for three days up to four weeks. Recovery begins within two to four weeks after the progression stops. While most patients recover, approximately 15%-20% of patients experience persistent symptoms. GBS is fatal in 5% of cases.

***Haemophilus influenzae* type b (Hib):** Bacteria responsible for diseases such as meningitis, epiglottitis, pneumonia and others.

Hay fever: An acute allergic nasal cold and eye inflammation.

Heart failure: A heart condition in which the ability of the heart to function is impaired.

Helper T cell: Type of lymphocyte that produces various cytokines that help to direct the immune response when stimulated by antigen.

Hemodialysis: Process of removing blood from an artery, purifying it by dialysis, adding vital substances and returning it to a vein.

Hemorrhagic: Escaping of large quantities of blood from a blood vessel or heavy bleeding.

Hemorrhagic fevers: Refers to a group of illnesses that are caused by several distinct families of viruses. Characteristically, these illnesses damage the overall vascular system, and cause the body's ability to regulate itself to become impaired. These symptoms are often accompanied by hemorrhage (bleeding); however, the bleeding is itself rarely life-threatening. While some types of hemorrhagic fever viruses can cause relatively mild illnesses, many of these viruses cause severe, life-threatening disease.

Hepatitis: A group of virus-caused diseases that cause fever, malaise that can lead to hospitalization, morbidity, complications and death.

Hepatitis A: A virus-caused disease with symptoms including anorexia, nausea and jaundice with a fatality rate of 0.3%.

Hepatitis B: A virus-caused disease with symptoms, including anorexia, nausea, vomiting, abdominal pain, jaundice and liver abnormalities. Chronically infected persons are at increased risk for developing liver failure and hepatocellular carcinoma.

Hepatocellular carcinoma: Cancer of the liver cells.

Herd immunity: See community immunity.

Herpes zoster: A disease characterized by painful skin lesions that occur mainly on the trunk (back and stomach) of the body but which can also develop on the face and in the mouth. Complications include headache, vomiting, fever and meningitis. Recovery may take up to five weeks. Herpes zoster is caused by the same virus that is responsible for chickenpox. Most people are exposed to this virus during childhood. After the primary infection (chickenpox), the virus becomes dormant, or inactivated. In some people the zoster reactivates years, or even decades later and causes herpes zoster. Also known as shingles.

Heterogeneous: Mixed. A heterogeneous population would consist of persons varying from one another by sex, race, age, etc.

Heterologous infections: Infections due to agents other than those targeted by vaccines.

Hexavalent vaccine: A vaccine that contains antigens from six different disease-causing agents.

Hib vaccine: Vaccine that protects children from *Haemophilus influenzae* type b disease.

Hives: Patchy, localized redness and swelling of the skin attributable to a variety of causes, including allergic reactions.

Homogeneous: Similar throughout. A homogeneous population would consist of persons who are identical or nearly identical in respects to such characteristics as sex, race, age, etc.

HOXA1: A gene that is involved in regulating the development of the brain.

Hygiene hypothesis: Proposed concept that immune system dysfunction is related to changes in antigen exposure (from actual disease, through the use of vaccines, etc.) during immune system development.

Hypersensitivity: A condition in which the body has an exaggerated immune response to a substance, e.g., food or drug. Also know as an allergy.

IgE: Immunoglobulin E. A class of proteins having antibody activity that is associated with asthma and allergic reactions.

Ileal-lymphoid-nodular hyperplasia: Swelling of lower abdominal lymph glands due to the increasing numbers of cells in the gland.

Immune response: Collective and coordinated response by the molecules and cells of the immune system that result in the elimination of naturally acquired disease-causing agents. This response also can be triggered by vaccination leading to immune protection against specific diseases.

Immune system: Tissues, cells and molecules found throughout the body that work together in a coordinated fashion to eliminate and prevent infections.

Immunity: Protection against a disease. There are two types of immunity, natural (innate) and acquired. Immunity is indicated by the presence of antibodies against a disease.

Immunization: The process by which a person or animal becomes protected against a disease. This term is often used interchangeably with vaccination or inoculation.

Immuno-competent: Having a working immune system.

Immunogenicity: The ability to produce a detectable immune response.

Immunogold electron microscopy: A research technique in which gold (electron-dense substance) is conjugated to antibody molecules that bind to specific antigens. This binding can be visualized by electron microscopy.

Immunosuppressed: When the immune system is unable to protect the body from disease. This condition can be caused by disease (like HIV infection or cancer) or by certain drugs (like those used in chemotherapy). Also known as immunocompromised.

Imported case: A case of a vaccine-preventable disease that occurs when an unvaccinated person is exposed to the disease-causing agent outside of the US and subsequently develops the disease while in the US.

Inactivated poliovirus (IPV) vaccine: Inactivated vaccine administered via injection that provides protection from polio.

Inactivated vaccine: A vaccine made from viruses and bacteria that have been killed through physical or chemical processes. These killed organisms cannot cause disease.

Incidence: The number of new disease cases reported in a population over a certain period of time.

Induration: The hardening of a normally soft tissue or organ, especially the skin, because of inflammation, infiltration of an abnormal growth or an accumulation of blood.

Inflammation: An influx of lymphocytes, macrophages and other cells into a site of injury or infection leading to redness and swelling at the site.

Inflammatory bowel disease: Inflammation of the lower gastrointestinal tract.

Influenza: Highly contagious viral infection of the nose, throat and lungs. Commonly known as the flu, this seasonal disease can be fatal to the aged, immunocompromised and infants.

Inhalational anthrax: Most severe and deadly form of anthrax disease that results when 8,000 to 50,000 anthrax bacteria spores enter the body through the airways.

Innate immunity: Immunity to microorganisms that does not require prior experience of the organism and does not depend on the generation of specific lymphocytes or the formation of specific antibodies.

***In situ* hybridization:** Technique used to identify a particular ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) sequence in the presence of many other sequences.

Institute of Medicine (IOM): Independent body established by the United States government, whose mission is to advance and disseminate scientific knowledge to improve human health.

Institutional Review Board (IRB): A committee of local experts established by the agency, institution or corporation conducting a clinical trial. The IRB is responsible for reviewing all aspects of the clinical trial.

Insulin: A chemical naturally produced by the pancreas that is involved in regulating glucose (sugar) metabolism. A deficiency of insulin causes diabetes.

Insulin-dependent diabetes mellitus (IDDM): Form of diabetes found primarily in children but has also been found in persons of all ages. Diabetes is a chronic health condition where the body is unable to produce insulin and properly breakdown sugar (glucose) in the blood. Also known as type 1 diabetes.

Interferon gamma: A whole-blood test for latent tuberculosis infection.

Interleukin 4 (IL-4): A T cell-derived cytokine that promotes B cell growth.

Interleukin 10 (IL-10): A cytokine that regulates the production of IgE antibodies that are responsible for allergic reactions.

Intussusception: Rare bowel obstruction that has recently been shown to be associated with the rotavirus vaccine.

***In utero*:** Before birth or in the uterus.

Invasive: Tending to invade healthy tissue.

Investigational New Drug (IND) application: Initial application to the United States Food and Drug Administration (FDA) that a vaccine manufacturer must complete to begin the process of vaccine licensure.

Investigational New Drug (IND) review: Stage of the vaccine licensure process that requires the vaccine sponsor to conduct clinical trials to provide data to the United States Food and Drug Administration (FDA) on the vaccine's safety and efficacy.

Japanese encephalitis (JE): A viral infection transmitted mainly by bites of a particular type of mosquito. JE is the leading cause of childhood encephalitis in Asia with approximately 35,000 cases and 10,000 deaths reported annually.

Jaundice: Yellow discoloration of the skin and mucous membranes that is often observed among hepatitis-infected persons.

Kuru: Human neurodegenerative disease associated with prions. This disease has only been reported among members of a small population native to Papua New Guinea and has since largely been eradicated.

Lesions: Abnormal changes in the structure of an organ or other body part due to injury or disease.

Live-attenuated vaccine: A vaccine consisting of a live virus that has been weakened through chemical or physical processes in order to produce an immune response without causing the severe effects of the disease. Attenuated vaccines currently licensed in the United States include measles, mumps, rubella, polio, yellow fever and varicella. Also known as an attenuated vaccine.

Liver: Organ in the upper abdomen that is responsible for many of the metabolic processes necessary to sustain life. This organ is particularly susceptible to infection by hepatitis viruses.

Liver failure: Disease state in which normal liver function is sufficiently impaired that its ability to sustain life is compromised.

Lumbar puncture: Procedure used to sample fluids surrounding the spinal cord.

Lymphatic system: The interconnected system of spaces and vessels between body tissues and organs by which serum and white blood cells circulate through the body.

Lymphatic tissue: See lymph glands/tissues.

Lymph glands/tissues: Organs and tissues that are composed of lymphocytes, macrophages and other cells involved in immunity. Many of the cellular interactions that occur during an immune response take place in lymph glands that include the spleen, thymus, tonsils and lymph nodes.

Lymphocytes: Small white blood cells that help the body defend itself against infection. These cells are produced in bone marrow and may develop into helper T cells, cytotoxic T cells or B cells that mature into antibody secreting plasma cells and other cells essential to immune competence.

Macrophage: A large cell that helps the body defend itself against disease by engulfing and destroying the foreign organisms, e.g., bacteria.

Magnetic resonance imaging: Diagnostic procedure that uses magnetic fields to produce images of organs and tissues in the body. Provides greater clarity and resolution than x-rays when examining these structures.

Major histocompatibility complex (MHC): Refers to a family of genes that code for proteins involved in antigen presentation and other interactions between cells of the immune system.

Malaise: A vague feeling of illness.

Measles: Highly contagious respiratory disease that is caused by a virus. Symptoms include rash, high fever, cough, runny nose and red, watery eyes. Severe complications can occur such as pneumonia, encephalitis, seizures and death.

Meningitis: Inflammation of the brain and spinal cord that can result in permanent brain damage and death.

Meningococcal disease: Leading cause of bacterial meningitis and sepsis in older children and young adults in the United States. Certain medical conditions, household crowding, chronic illness and smoking increase the risk of developing this disease.

Meta-analysis: A statistical approach to analyzing data from numerous individual studies for the purpose of integrating the findings.

Metabolic: The entire spectrum of biological and chemical processed occurring in an organism, particularly those relating to the production and use of energy in the body.

Metabolic disorder: Abnormality or disease that results from a defect in gene expression or regulation. Examples include Tay-Sachs disease, sickle cell disease, and various diseases affecting the nervous system.

Methyl mercury: A chemical contaminant found in some seafood, high doses of this type of mercury have been associated with health effects, particularly among infants whose mothers were exposed during pregnancy. Several federal agencies in the United States, including the Environmental Protection Agency (EPA), Agency for Toxic Substance and Disease Registry (ATSDR) and the Food and Drug Administration (FDA), have developed guidelines for limiting intake of methyl mercury.

MMR vaccine: A combination vaccine that protects persons from developing measles, mumps and rubella.

Molecular mimicry: The sharing of biochemical and/or structural similarities by two distinct molecules. Typically used in the context of explaining why antibodies against a disease-causing agent cross-react with a self antigen.

Monovalent: A vaccine containing a single antigen from a disease-causing organism.

Morbidity: Relative new cases of disease reported over time.

Multiple sclerosis: Chronic, often disabling disease of the central nervous system. Symptoms may be mild such as numbness in the limbs or severe such as paralysis or loss of vision. Most people with this disease are diagnosed between the ages of 20 and 40.

Mumps: Viral disease that usually begins with swollen salivary glands and can lead to swelling of the testicles in adolescents and adults, deafness, aseptic meningitis and death.

Myalgia: Muscle pain or tenderness.

Myelin: A soft, white, somewhat fatty material that forms a sheath around a nerve fiber.

Nausea: A sick feeling in the stomach, with an impulse to vomit.

***Neisseria meningitidis*:** Round-shaped bacteria that cause meningococcal disease.

Neonate: A newborn infant.

Nervous system: All of the nerve cells and nervous tissues in the body, including the brain, spinal cord, nerves, etc.

Neurodegenerative disease: Disease that causes a breakdown in the normal functions of the nervous system over time.

Neurodevelopmental disorder: Diseases of the nervous system that result from impaired development of the cells and tissues of the nervous system during fetal and postnatal development.

Neurologic disorder: Of, or affecting the nervous system. Examples includes seizures and encephalitis.

Neuropeptide: A small molecule that influences the biological activity of nerve cells and tissues.

Neurotrophin: A chemical that is attracted to cells or tissues of the nervous system.

Nodules: A small mass of rounded or irregular shape.

Non-obese diabetic (NOD) mice: An inbred strain of mice that is genetically predisposed to developing diabetes and is used in experimental animal studies.

Odds ratio: In a case-control study, the odds ratio is the ratio of the chance that cases were exposed to the proposed risk factor compared with the odds that the controls were exposed to this same factor. In a cohort study, the odds ratio is the comparison of the odds of developing a disease in persons exposed to a proposed risk factor compared with the odds of development of disease in persons non-exposed to the factor.

Oral poliovirus (OPV) vaccine: Attenuated vaccine administered via oral drops that provides protection from polio.

Pancreas: A long, irregularly shaped gland, lying behind the stomach, that secretes certain digestive enzymes into the intestine and hormones such as insulin into the bloodstream.

Pandemic: An epidemic occurring over a very large area.

Pathogens: Organisms, e.g., bacteria, viruses, parasites and fungi, that cause disease in human beings.

Pathogenesis: The mechanisms and processes resulting in the development of disease.

Pathology: A symptom or sign that is indicative of disease.

Penicillin: The first commercially available antibiotic used to treat infectious diseases. Introduced in the 1940s, penicillin was the principle weapon that physicians used against bacterial infections for many years.

Pentavalent vaccine: Vaccine that contains antigens from five different disease-causing agents.

Peripheral blood mononuclear cells: White blood cells containing a single nucleus that are ordinarily found circulating in the blood vessels, i.e., arteries and veins. These cells can leave the blood vessels and enter injured or infected tissues.

Pertussis: Highly contagious respiratory disease causing a severe "barking" cough that often occurs in spasms, making it difficult to eat, drink or sleep.

Pervasive developmental disorder: A non-specific type of autism-spectrum disorder.

Phase I study: A clinical trial involving a small number of healthy persons that is used to determine if a vaccine can be safely administered to humans and if it elicits an immune response in the study participants.

Phase II study: A clinical trial involving a larger number of healthy persons that is used to determine the appropriate dose and schedule for administering the vaccine, and to assess its effectiveness in preventing disease.

Phase III study: A clinical trial involving many thousands of persons that is used to demonstrate the safety and efficacy of a vaccine in a large, diverse population.

Placebo: An inert or inactive substance used in controlled experiments to test the efficacy, safety, involvement, activity, etc. of another substance (such as a drug or vaccine).

Placebo studies: A study utilizing an inactive substance or treatment (placebo) that has no effect on human beings in order to compare the clinical response to this substance or treatment with the active agent.

Pneumococcal disease: Bacterial disease that causes bacteremia, pneumonia, sinusitis, meningitis and severe ear infections. This disease is most common is children less than two years of age and adults over 40 years of age, and occurs more often in males than in females at all ages.

Pneumococcal polysaccharide: Vaccine comprised of multiple chains of sugar molecules derived from the bacteria Streptococcus pneumoniae that protects against pneumonia, bacteremia and meningitis caused by that organism.

Pneumonia: Inflammation of the lungs characterized by fever, chills, muscle stiffness, chest pain, cough, shortness of breath, rapid heart rate and difficulty breathing.

Poliomyelitis (polio): Infectious viral disease that attacks the central nervous system and can cause paralysis, muscle atrophy and death. Polio spreads to unaffected individuals by contact with an infected person or their stool. Symptoms can include flu-like illness, muscle pain or stiffness and transient or permanent paralysis.

Poliomyelitis Eradication Initiative: Worldwide campaign to eradicate polio through the use of polio vaccines.

Polymerase chain reaction (PCR): Highly specific research procedure that results in a geometric amplification of a specific deoxyribonucleic acid (DNA) sequence that facilitates the subsequent identification and characterization of that sequence.

Polymerase protein: An enzyme that facilitates the linkage of similar molecules to form a chain or polymer.

Polysaccharide: Long chains of sugar molecules that form unique structures on the surfaces of many infectious agents.

Polysaccharide vaccine: Vaccines that are composed of long chains of sugar molecules that resemble the surface of certain types of bacteria. Polysaccharide vaccines are available for pneumococcal disease, meningococcal disease and *Haemophilus influenzae* type b.

Pre-clinical study: A study conducted in animals to evaluate the effectiveness and safety of candidate vaccines or other pharmaceutical compounds.

Preservative: An additive that protects vaccine against contamination or spoilage.

Prevalence: The number of disease cases (new and existing) within a population over a given period of time.

Prion: Abnormal form of a protein found in brain cells that is capable of causing a cell to produce more abnormal protein. The presence of the abnormal protein is associated with fatal neurodegenerative changes.

Prophylaxis: Measures designed to preserve health and prevent the spread of disease.

Prospective cohort studies: Cohort studies in which researchers follow disease progression in study participants beginning at the start of the trial.

Protein: Large, complex molecules that are largely responsible for the complex and diverse functions associated with living organisms.

Rabies: A viral infection transmitted to humans by a scratch or a bite of an infected animal or the exchange of the infected animal's saliva to a human mucous membrane (lining of nose or mouth, open wound, etc.). Disease occurs after the rabies virus invades the victim's central nervous system, causing inflammation of the brain and spinal cord and rapid progression to paralysis, coma and death.

Rabies immune globulin: Solution of derived blood plasma of adult human donors who have been immunized with rabies vaccine.

Reactogenicity: Refers to the common reactions associated with vaccine use. These typically include redness, swelling or tenderness at the injection site or mild fever. Vaccine developers and regulators work to minimize the reactogenicity of all licensed vaccines.

Recombinant DNA technology: The technique by which genetic material from one organism is inserted into a foreign cell or another organism in order to mass-produce the protein encoded by the inserted genes.

Registry: A database for tracking the immunization records of individuals that facilitates determination of the individual's vaccination history to ensure that all doses of all of the Advisory Committee on Immunization Practices' (ACIP's) recommended vaccines are administered on time.

Relative risk: The ratio of the risk of disease in persons exposed to the proposed risk factor compared to the risk of disease in persons unexposed to the proposed risk factor.

Rendering: Animal carcasses and meat processing wastes are milled and decomposed by boiling at high pressures. This procedure produces a liquid protein under a layer of fat. The fat is removed and the liquid protein is dried into a meat and bone meal product that is packaged and distributed.

Retrospective cohort studies: Cohort studies in which researchers use past historical data to frame a study period and obtain findings. Exposure to the proposed risk factor is determined using these records and data on whether the study participants have developed the disease is taken either from past records or at the beginning of the study.

Rheumatic fever: Respiratory tract infection associated with inflammation of the heart and other organs that can trigger autoimmune heart disease in some patients.

Rheumatic heart disease: Damage to the valves of the heart caused by antibodies associated with group A streptococcus infections.

Ribonucleic acid (RNA): A long, unbranched molecule of nucleotides containing ribose that is transcribed from deoxyribonucleic acid (DNA) and is necessary for the production of proteins.

Risk: The likelihood that an individual will experience a certain event.

Rotavirus vaccine: Vaccine to protect against rotavirus, a severe diarrheal illness in childhood that accounts for more than 500,000 physician visits and approximately 50,000 hospitalizations each year among children less than five years of age. Symptoms include fever, an upset stomach and vomiting followed by diarrhea that may lead to dehydration.

Rubella: Mild rash illness when contracted by adult males and children. In women, rubella can cause arthritis, arthralgia and can cause serious birth defects or death to developing fetuses.

Safety assessment: The process of examining all available scientific information relevant to determining the safety of a vaccine, recognizing that there may be uncertainties associated with that information that need to be considered. Because safety is not absolute, the assessment addresses both the health benefits of the vaccine as well as possible health hazards that it may pose.

Salivary glands: Glands found in the mouth that release fluids and proteins that aid in digestion and swallowing.

***Salmonella typhi*:** Rod-shaped bacteria that cause typhoid fever.

Scarification: The making of small breaks, punctures or scratches in the skin. This technique is used for delivery of smallpox vaccine into the body of a vaccinee.

Scrapie: Spongiform encephalopathy disease caused by a prion that has been observed in sheep for over 200 years.

Seizure: The sudden onset of a jerking and staring spell usually caused by fever. Also known as convulsion.

Selection bias: Occurs in a study if the way in which cases and controls or exposed and non-exposed individuals were selected is such that an apparent association is observed—even if, in reality, exposure and disease are not associated.

Sepsis: Toxic condition resulting from the spread of bacteria or their products from a point of infection.

Septic arthritis: Arthritis resulting from the spread of bacteria or their products from a point of infection.

Serotype: The set of antigens characteristic of a group of related organisms.

Serum: A gold-colored, protein-rich fluid that carries blood cells through the arteries and veins.

Shaken Baby Syndrome (SBS): A serious form of child maltreatment resulting in neurologic damage, usually involving infants less than six months of age.

Shingles: A disease characterized by painful skin lesions that occur mainly on the trunk (back and stomach) of the body but which can also develop on the face and in the mouth. Complications include headache, vomiting, fever and meningitis. Recovery may take up to five weeks. Shingles is caused by the same virus that is responsible for chickenpox. Most people are exposed to this virus during childhood. After the primary infection (chickenpox), the virus becomes dormant or inactivated. In some people, the infection reactivates years, or even decades later and causes shingles. Also known as herpes zoster.

Sinusitis: Inflammation of the nasal or other sinuses.

Smallpox: Serious infectious disease that caused rash, formation of pustules and scarring. Serious cases resulted in hemorrhaging and death. Smallpox vaccine use has led to the eradication of this disease worldwide.

Solvents: Fluids in which other materials are dissolved.

Spanish flu: Name applied to the 1918 global influenza epidemic that resulted in an estimated 21 million deaths.

Spasm: An involuntary and abnormal muscle contraction.

Specific acquired immunity: The production of antibodies and/or cytotoxic T cells against a specific disease by the immune system. Active immunity can be acquired in two ways, either by contracting the disease or through vaccination. Active immunity is usually permanent, meaning an individual is protected from the disease for the duration of their lives.

Steroids: A class of compounds that include medicines used to treat various conditions, including inflammation. Some of these drugs are used to suppress the immune response in the context of organ transplantation or chronic autoimmune disease.

***Streptococcus pneumoniae*:** Round infectious bacteria that cause pneumonia, bacteremia and meningitis.

Sudden Infant Death Syndrome (SIDS): The sudden and unexpected death of a healthy infant under one year of age.

Subunit vaccines: Inactivated vaccine that utilizes fractional parts of antigens to generate an immune response.

Superantigens: Antigen that, following processing by a macrophage, becomes able to stimulate an immune response even at very low concentrations.

Systemic: Affecting the body generally.

T cell: A type of lymphocyte that is responsible for several distinct immune functions. T helper cells coordinate and regulate immune responses. T cytotoxic cells identify and destroy certain types of disease-causing agents and virus-infected cells.

T helper 1 (Th1) cell: A type of helper T cell that releases certain cytokines that promote the development of protective antibodies.

T helper 2 (Th2) cell: A type of helper T cell that releases certain cytokines that promote the development of IgE antibodies that are associated with allergic reactions.

Temporal relationship: Guideline for evaluating an association between a vaccine and an adverse event that asks the question or whether exposure to the vaccine occurred before the adverse event developed.

Testicles: Male reproductive organs.

Tetanus: Disease of the nervous system caused by a toxic chemical produced by an infectious agent that makes the muscles spasm. Also known as lockjaw.

Thalidomide: A sedative and hypnotic drug that was withdrawn from the market after it was found to cause severe birth defects when taken during pregnancy.

Thimerosal: Preservative used in some vaccines and other products since the 1930s as a safeguard against product contamination. For example, without use of a preservative such as thimerosal, vaccine vials that are used for multiple immunization could become contaminated between injections.

Threshold: A certain level of exposure above which disease will develop.

Thrombocytopenia: An abnormal decrease in the number of platelets (cells that allow the blood to clot) in circulating blood.

Tonsil: Lymph glands found in the throat at the back of the mouth.

Toxic shock syndrome: This disease is characterized by sudden onset of fever, chills, vomiting, diarrhea, muscle pains and rash. Toxic shock syndrome has been associated with use of tampons and intravaginal contraceptive devices in women and occurs as a complication of skin abscesses or surgery. Approximately 5% of cases will die from this disease.

Toxin: A type of chemical produced by certain disease-causing agents such as *Clostridium tetani* that causes disease. The *Clostridium tetani* toxin causes tetanus.

Type I diabetes: Form of diabetes found primarily in children but has also been found in persons of all ages. Diabetes is a chronic health condition where the body is unable to produce insulin and properly breakdown sugar (glucose) in the blood. Also known as insulin-dependent diabetes mellitus.

Typhoid fever: Acute generalized infection that is caused by the bacterium *Salmonella typhi*. Severe forms of the disease are characterized by persistent high fever, abdominal discomfort, malaise and headache. Transmission of typhoid fever occurs in areas where sanitation is primitive and where water supplies are not treated.

Ulcerative colitis: A chronic illnesses that can inflame the entire large intestine and rectum causing bloody diarrhea, abdominal pain and weight loss.

Vaccination registry: Confidential, computerized information systems that catalog patients' immunization histories. Immunization registries provide information that can be utilized for vaccine safety studies and incorporated into ongoing quality improvement practices.

Vaccine: A preparation of killed or attenuated disease-causing agents or their component proteins or other molecules that is used to stimulate a person's immune system in order to protect that person from developing a specific disease.

Vaccine Adverse Events Reporting System (VAERS): Mechanism by which information about adverse events following immunization may be reported, analyzed and made available to the public.

Vaccinees: Persons who have been vaccinated.

Vaccine Identification Standards Initiative (VISI): Requires the placement of a bar-coded sticker on each vaccine produced so that health professionals can peel off the sticker and place it on the immunization record of the person being evaluated.

Vaccine information statement (VIS): Statements that outline the benefits and risks of vaccination and give information on how to report adverse events following immunization to the Vaccine Adverse Events Reporting System (VAERS). Health professionals are required by law to give all persons who are to be vaccinated or their guardians a copy of the corresponding vaccine information statement.

Vaccine Injury Compensation Program (VICP): Provides compensation to children who have been injured from a vaccine administered as part of the routine immunization schedule.

Vaccine Safety Datalink (VSD) Project: In order to increase knowledge about vaccine adverse events, the Centers for Disease Control and Prevention (CDC) have formed partnerships with large health maintenance organizations (HMOs) to continually evaluate vaccine safety. The project contains data on more than six million people. Medical records are monitored for potential adverse events following immunization. This project allows for planned vaccine safety studies as well as timely investigations of hypotheses.

Vaccine schedule: Recommendations developed by the Advisory Committee on Immunization Practices (ACIP) that specify the appropriate times for administering approved vaccines to infants, children, adolescents and adults.

Vaccine sponsor: An individual physician, university, hospital, government agency or commercial firm/manufacturer who pays or bears responsibility for a vaccine's research and development.

Vaccinia: Acute infection caused by the vaccinia virus and characterized by a localized pustular eruption. The infection stimulates antibody production which confers immunity to smallpox. A live vaccinia virus preparation is used as an active immunizing agent against smallpox.

Valent: Refers to the number of antigenic components of a vaccine.

Varicella: A severe, contagious viral infection, which is characterized by red blotches appearing on the skin. The infection is transmitted by airborne droplets and direct contact with lesions. Complications include bacterial infection of skin lesions, pneumonia, dehydration, hospitalization and death. Also known as chickenpox.

Variola virus: Virus that causes smallpox disease.

Virino: A small, informational molecule (likely a nucleic acid) associated with a protein.

Virus: A tiny organism that multiplies within cells and causes diseases such as chickenpox, measles, mumps, rubella, pertussis and hepatitis. Viruses are not affected by antibiotics, the drugs used to kill bacteria.

White blood cells: Found in the blood, these cells are responsible for keeping the bloodstream and tissues free of pathogens, abnormal cells and other unwanted material.

Whooping cough: Another name for pertussis.

Wild-type: Naturally-occurring form of the pathogen.

Yellow fever: Disease caused by a ribonucleic acid (RNA) virus transmitted to humans by mosquitoes or ticks. The severity of this disease ranges from flu-like symptoms to severe hepatitis and hemorrhagic fever. This disease kills an estimated 30,000 people per year and occurs only in sub-Saharan Africa, where the majority of cases are reported, and in tropical South America.

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ACRONYMS

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
ADEM	Acute disseminated encephalomyelitis
AIDS	Acquired Immune Deficiency Syndrome
ASD	Autism-spectrum disorder
ATSDR	Agency for Toxic Substances and Disease Registry
BLA	Biologics License Application
BSE	Bovine spongiform encephalopathy
CBER	Center for Biologics Evaluation and Research (FDA)
CDC	Centers for Disease Control and Prevention
CGMP	Current Good Manufacturing Practices
CISA	Clinical Immunization Safety Assessment
CJD	Creutzfeldt-Jakob disease
CMS	Centers for Medicare and Medicaid Services
COID	Committee on Infectious Diseases (AAP)
CRS	Congenital rubella syndrome
DEET	N,N-diethyl-m-toluamide
DHHS	Department of Health and Human Services (US)
DNA	Deoxyribonucleic acid
DoD	Department of Defense
DTaP	Diphtheria-tetanus-acellular pertussis
DTP	Diphtheria-tetanus-whole cell pertussis
EAE	Experimental autoimmune encephalomyelitis
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
HAV	Hepatitis A virus
HAVRIX®	Hepatitis A vaccine (GlaxoSmithKline)
HBV	Hepatitis B virus
Hib	*Haemophilus influenzae* type b
HIV	Human Immunodeficiency Virus
HMO	Health maintenance organization
HRSA	Health Resources and Services Administration
IAVG	Interagency Vaccine Group
IBD	Inflammatory bowel disease
IDDM	Insulin-dependent diabetes mellitus
IgE	Immunoglobulin E
IL-4	Interleukin 4
IL-10	Interleukin 10
IND	Investigational New Drug
IOM	Institute of Medicine
IPV	Inactivated poliovirus
IRB	Institutional Review Board
JE	Japanese encephalitis
MCV	Measles-containing vaccine
MHC	Major histocompatibility complex
MMR	Measles, mumps, rubella
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSAEFI	Monitoring System for Adverse Events Following Immunization
NCES	National Childhood Encephalopathy Study
NIH	National Institutes of Health
NOD	Non-obese diabetic
NVAC	National Vaccine Advisory Committee
nvCJD	New variant Creutzfeldt-Jacob disease
NVPO	National Vaccine Program Office
OGC	Office of the General Counsel
OPV	Oral poliovirus
PAHO	Pan American Health Organization
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PHS	Public Health Service (US)
RIG	Rabies immune globulin
RNA	Ribonucleic acid
SBS	Shaken Baby Syndrome
SIDS	Sudden Infant Death Syndrome
USAID	United States Agency for International Development
VAERS	Vaccine Adverse Events Reporting System
VAQTA®	Hepatitis A vaccine (Merck & Co.)
vCJD	Variant Creutzfeldt-Jacob disease
VISI	Vaccine Identification Standards Initiative
VIS	Vaccine information statement
VICP	Vaccine Injury Compensation Program
VIG	Vaccinia immune globulin
VRBPAC	Vaccines and Related Biological Products Advisory Committee (CBER)
VSD	Vaccine Safety Datalink Project
WHO	World Health Organization